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(FILE 'HOME' ENTERED AT 09:32:15 ON 18 JAN 2001)

FILE 'MEDLINE' ENTERED AT 09:33:52 ON 18 JAN 2001

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E MYELOCYTES/CT
E LYMPHOCYTE/CT
E LYMPHOCYTES/CT
E E3+AKK
E E3+ALL
E BLOOD CELLS/CT
E E3+NT
E E17+NT
E E1+ALL
L1      363287 S LEUKOCYTES+NT/CT
L2      36221 S APOPTOSIS
L3      6901 S L1 AND L2
          E ANTIBODIES, MONOCLONAL+NT/CT
L4      97011 S ANTIBODIES, MONOCLONAL+NT/CT
L5      529 S L4 AND L3
L6      12436 S INTEGRIN#
L7      22 S L5 AND L6
L8      97 S L1 AND L2 AND L6
L9      37 S L8 AND ANTIBOD?
L10     120260 S LEUKEMIA+NT/CT
L11     392 S L10 AND L3
L12     36 S L11 AND L4
L13     2 S L12 AND L6
L14     40242 S L10 (L) TH./CT
L15     80 S L14 AND L2 AND L1
L16     4 S L15 AND L4
L17     26 S L7 OR L13 OR L16

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=> d .med 1-26

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L17 ANSWER 1 OF 26 MEDLINE
AN 2000261985 MEDLINE
DN 20261985
TI Molecular characterization of the surface of apoptotic neutrophils:
    implications for functional downregulation and recognition by
    phagocytes.
AU Hart S P; Ross J A; Ross K; Haslett C; Dransfield I
CS The Rayne Laboratory, Respiratory Medicine Unit, University of Edinburgh
    Medical School, Teviot Place, Edinburgh, EH8 9AG, UK.
SO CELL DEATH AND DIFFERENTIATION, (2000 May) 7 (5) 493-503.
    Journal code: C7U. ISSN: 1350-9047.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200009
EW 20000905
AB We have used a panel of monoclonal antibodies and lectins to examine the
    profile of surface molecule expression on human neutrophils that have
    undergone spontaneous apoptosis during in vitro culture.

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Neutrophil **apoptosis** was found to be accompanied by down-regulation of the immunoglobulin superfamily members PECAM-1 (CD31), ICAM-3 (CD50), CD66acde, and CD66b and the **integrin**-associated proteins CD63 and urokinase plasminogen activator receptor (CD87) that may

alter the potential for adhesive interactions. Cellular interactions may be further influenced by the reduction of the expression of surface carbohydrate moieties, including sialic acid. Reduced expression of FcgammaRII (CD32), complement receptor type 1 (CD35) and receptors for pro-inflammatory mediators C5a (CD88) and TNFalpha (CD120b) associated with **apoptosis** might limit neutrophil responsiveness to stimuli that trigger degranulation responses. Although many of the receptors we have examined are expressed at reduced levels on apoptotic neutrophils,

we found that there was differential loss of certain receptors (e.g. CD16, CD15 and CD120b) and increased expression of aminopeptidase-N (CD13). Together with our previous data showing that expression of certain molecules e.g. LFA-3 (CD58) is not altered during neutrophil **apoptosis**, these data are suggestive of specific changes in receptor mobilisation and shedding associated with **apoptosis**. Although reduced expression of CD63 (azurophilic granules) and CR1 (specific granules) indicates that granule mobilisation does not accompany

**apoptosis**, a monoclonal antibody (BOB78), that recognises a 90 kDa antigen localised in intracellular granules, defines a subpopulation of apoptotic neutrophils that exhibit nuclear degradation yet retain intact plasma membranes. BOB78 positive neutrophils were found to bind biotinylated thrombospondin, suggesting that this mAb defines surface molecular changes associated with exposure of thrombospondin binding moieties.

CT Check Tags: Animal; Human; In Vitro; Support; Non-U.S. Gov't

**Antibodies, Monoclonal**

**Apoptosis: IM, immunology**

**\*Apoptosis: PH, physiology**

Carbohydrates: ME, metabolism

Cell Membrane: IM, immunology

Cell Membrane: ME, metabolism

Down-Regulation (Physiology)

**\*Neutrophils: CY, cytology**

**Neutrophils: IM, immunology**

**\*Neutrophils: ME, metabolism**

Phagocytes: CY, cytology

Phagocytes: IM, immunology

Phagocytes: ME, metabolism

Phenotype

Receptors, Cell Surface: ME, metabolism

Thrombospondins: ME, metabolism

L17 ANSWER 2 OF 26 MEDLINE

AN 2000253142 MEDLINE

DN 20253142

TI Interaction of merosin (laminin 2) with very late activation antigen-6 is necessary for the survival of CD4+ CD8+ immature thymocytes.

AU Iwao M; Fukada S; Harada T; Tsujikawa K; Yagita H; Hiramane C; Miyagoe Y; Takeda S; Yamamoto H

CS Department of Immunology, Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka, Japan.

SO IMMUNOLOGY, (2000 Apr) 99 (4) 481-8.  
Journal code: GH7. ISSN: 0019-2805.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 200008

EW 20000801

AB The laminin alpha2-chain is a component of merosin, a member of the laminin family molecules, which is mainly expressed in the basement membranes of striated muscle. It is known that laminin alpha2 gene (lama2) null mutant mice (dy3k/dy3k) exhibit congenital muscular dystrophy (CMD). Because the laminin alpha2-chain is also expressed in the thymus, the role of merosin in the thymus was examined. In association with the onset of muscular dystrophy, CD4+ CD8+ double-positive (DP) thymocytes disappear by apoptotic cell death, while CD4+ CD8- or CD4- CD8+ thymocytes remain. In order to study the mechanisms leading to the selective death of DP cells in the absence of merosin, the role of the interaction between very late activation antigen-6 (VLA-6), a candidate merosin ligand in the thymus, and merosin was examined. The in vitro survival of thymocytes from normal mice was maintained by the addition of either anti-VLA-6 monoclonal antibodies (mAbs) or merosin. Furthermore, when the normal thymocytes were cultured on thymic epithelial cell lines, viable DP cell recoveries on wild-type epithelial cells were better than on cells from null mutant mice. The results suggest that DP cells are more sensitive to an uncharacterized apoptotic death signal, and that survival is supported by the interaction between VLA-6 and merosin.

CT Check Tags: Animal; Support, Non-U.S. Gov't  
**Antibodies, Monoclonal: PD, pharmacology**  
**Apoptosis: DE, drug effects**  
Cell Survival: DE, drug effects  
Cells, Cultured  
**CD4-Positive T-Lymphocytes: ME, metabolism**  
**CD4-Positive T-Lymphocytes: PA, pathology**  
**CD8-Positive T-Lymphocytes: ME, metabolism**  
**CD8-Positive T-Lymphocytes: PA, pathology**  
Epithelium: ME, metabolism  
Gene Deletion  
**Integrins: IM, immunology**  
**\*Integrins: ME, metabolism**  
Laminin: AN, analysis  
Laminin: GE, genetics  
**\*Laminin: PD, pharmacology**  
Mice  
Mice, Inbred BALB C  
Mice, Mutant Strains  
**\*Muscular Dystrophy, Animal: IM, immunology**  
**\*T-Lymphocytes: ME, metabolism**  
**T-Lymphocytes: PA, pathology**  
Thymus Gland: CH, chemistry  
Thymus Gland: IM, immunology

AN 1999445392 MEDLINE  
 DN 99445392  
 TI Resting and cytokine-stimulated human small airway epithelial cells recognize and engulf apoptotic eosinophils.  
 AU Walsh G M; Sexton D W; Blaylock M G; Convery C M  
 CS Department of Medicine & Therapeutics, University of Aberdeen Medical School, Aberdeen, UK.. g.m.walsh@abdn.ac.uk  
 SO BLOOD, (1999 Oct 15) 94 (8) 2827-35.  
 Journal code: A8G. ISSN: 0006-4971.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
 EM 200001  
 EW 20000104  
 AB Eosinophils, which are prominent cells in asthmatic inflammation, undergo **apoptosis** and are recognized and engulfed by phagocytic macrophages in vitro. We have examined the ability of human small airway epithelial cells (SAEC) to recognize and ingest apoptotic human eosinophils. Cultured SAEC ingested apoptotic eosinophils but not freshly isolated eosinophils or opsonized erythrocytes. The ability of SAEC to ingest apoptotic eosinophils was enhanced by interleukin-1alpha (IL-1alpha) or tumor necrosis factor alpha (TNFalpha) in a time- and concentration-dependent fashion. IL-1alpha was found to be more potent than TNFalpha and each was optimal at 10(-10) mol/L, with a significant (P <.05) effect observed at 1 hour postcytokine incubation that was maximal at 5 hours. IL-1alpha stimulation not only increased the number of SAEC engulfing apoptotic eosinophils, but also enhanced their capacity for ingestion. The amino sugars glucosamine, n-acetyl glucosamine, and galactosamine significantly inhibited uptake of apoptotic eosinophils by both resting and IL-1alpha-stimulated SAEC, in contrast to the parent sugars glucose, galactose, mannose, and fucose. Incubation of apoptotic eosinophils with the tetrapeptide RGDS, but not RGEs, significantly inhibited their uptake by both resting and IL-1alpha-stimulated SAEC, as did monoclonal antibody against alpha5beta1 and CD36. Thus, SAEC recognize apoptotic eosinophils via lectin- and **integrin**-dependent mechanisms. These data demonstrate a novel function for human bronchial epithelial cells that might represent an important mechanism in the resolution of eosinophil-induced asthmatic inflammation.  
 CT Check Tags: Comparative Study; Human; Support, Non-U.S. Gov't  
 Acetylglucosamine: PD, pharmacology  
**Antibodies, Monoclonal: PD, pharmacology**  
 Antigens, CD36: PH, physiology  
**\*Apoptosis**  
 \*Bronchi: CY, cytology  
 Bronchi: DE, drug effects  
 Cells, Cultured  
 Dose-Response Relationship, Drug  
**\*Eosinophils**  
 Epithelial Cells: DE, drug effects  
 Epithelial Cells: PH, physiology  
 Erythrocytes  
 Galactosamine: PD, pharmacology  
 Glucosamine: PD, pharmacology  
 Hexoses: PD, pharmacology

\*Interleukin-1: PD, pharmacology  
 Oligopeptides: PD, pharmacology  
 Opsonins  
 \*Phagocytosis  
 Receptors, Vitronectin: AI, antagonists & inhibitors  
 Receptors, Vitronectin: PH, physiology  
 Recombinant Proteins: PD, pharmacology  
 \*Tumor Necrosis Factor: PD, pharmacology

L17 ANSWER 4 OF 26 MEDLINE  
 AN 1999441380 MEDLINE  
 DN 99441380  
 TI Activated lymphocytes promote endothelial cell detachment from matrix: a role for modulation of endothelial cell beta 1 **integrin** affinity.  
 AU Phan C; McMahon A W; Nelson R C; Elliott J F; Murray A G  
 CS Department of Medicine, University of Alberta, Edmonton, Canada.  
 SO JOURNAL OF IMMUNOLOGY, (1999 Oct 15) 163 (8) 4557-63.  
 Journal code: IFB. ISSN: 0022-1767.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
 EM 200001  
 EW 20000104  
 AB In vivo, MHC class I-restricted injury of allogeneic tissue or cells infected by intracellular pathogens occurs in the absence of classical cytolytic effector mechanisms and Ab. Modulation of the target cell adhesion to matrix may be an additional mechanism used to injure vascular or epithelial cells in inflammation. We studied the mechanisms of human umbilical vein endothelial cell (EC) detachment from matrix-coated plastic following contact by concanamycin A-treated lymphocytes as an in vitro model of perforin-independent modulation of EC basement membrane adhesion. Human PBL were depleted of monocytes, stimulated, then added to an EC monolayer plated on either fibronectin or type I collagen matrices. Activated, but not resting, PBL induced progressive EC detachment from the underlying matrix. Injury of the EC monolayer required direct cell contact with the activated lymphocytes because no detachment was seen when the PBL were placed above a Transwell membrane. Moreover plasma membranes prepared from activated but not resting PBL induced EC detachment. Adherent EC stimulated with activated PBL did not show evidence of **apoptosis** using TUNEL and annexin V staining at time points before EC detachment was observed. Finally, neither the matrix metalloproteinase inhibitors o-phenanthroline and BB-94 nor aprotinin blocked EC detachment. However, activation of EC beta1 **integrin** using mAb TS2/16 or Mg2+ decreased EC detachment. These data indicate that cell-cell contact between activated PBL and EC reduces adhesion of EC to the underlying matrix, at least in part by inducing changes in the affinity of the endothelial beta 1 **integrin**.  
 CT Check Tags: Human; Support, Non-U.S. Gov't

Adjuvants, Immunologic: PH, physiology  
**Antibodies, Monoclonal: PD, pharmacology**  
 Antigens, CD29: IM, immunology  
 \*Antigens, CD29: PH, physiology  
**Apoptosis: IM, immunology**  
 Cell Adhesion: IM, immunology  
 Cell Communication: IM, immunology  
 Cells, Cultured  
 Cytotoxicity, Immunologic: IM, immunology  
 \*Endothelium, Vascular: CY, cytology  
 Endothelium, Vascular: EN, enzymology  
 \*Endothelium, Vascular: IM, immunology  
 Endothelium, Vascular: PH, physiology  
 Extracellular Matrix: EN, enzymology  
 \*Extracellular Matrix: IM, immunology  
 \*Lymphocyte Transformation: IM, immunology  
**Lymphocytes: EN, enzymology**  
**\*Lymphocytes: IM, immunology**  
**Lymphocytes: PH, physiology**  
 Matrix Metalloproteinases: PH, physiology  
 Umbilical Veins

L17 ANSWER 5 OF 26 MEDLINE

AN 1999244923 MEDLINE

DN 99244923

TI Endothelial expression of VCAM-1 in experimental crescentic nephritis and effect of antibodies to very late antigen-4 or VCAM-1 on glomerular injury.

AU Allen A R; McHale J; Smith J; Cook H T; Karkar A; Haskard D O; Lobb R R; Pusey C D

CS Renal Section, Division of Medicine, British Heart Foundation Cardiovascular Medicine Unit, National Heart and Lung Institute, Imperial College School of Medicine, London, United Kingdom.. a.allen@rpms.ac.uk

SO JOURNAL OF IMMUNOLOGY, (1999 May 1) 162 (9) 5519-27.

Journal code: IFB. ISSN: 0022-1767.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199907

EW 19990704

AB The migration of leukocytes into glomeruli in crescentic glomerulonephritis is fundamental to pathogenesis, and offers important therapeutic opportunities. We addressed the importance of VCAM-1, and its leukocyte ligand very late antigen-4 (VLA-4), in such leukocyte migration.

In a rat model of nephrotoxic nephritis, glomerular expression of VCAM-1, studied by immunohistochemistry, was up-regulated by day 6 of nephritis. To quantify kidney endothelial VCAM-1 expression, a differential radiolabeled mAb technique was used, which demonstrated that protein expression was not up-regulated by day 2 of nephritis, but rose threefold between days 2 and 5, and remained elevated until at least day 28. An in vivo study was then performed, using blocking mAbs to either VCAM-1 or VLA-4, starting mAb treatment on the day prior to disease induction, and continuing until animals were sacrificed at day 7. mAbs to VLA-4 significantly attenuated renal injury (albuminuria, glomerular fibrinoid necrosis, and crescent formation), but mAbs to VCAM-1 had no significant

effect. Surprisingly, the number of leukocytes within glomeruli was unaffected by anti-VLA-4 mAb therapy, despite the reduction in renal injury. Paradoxically, classical markers of macrophage activation were increased in the anti-VLA-4- and anti-VCAM-1-treated animals. This study demonstrates that kidney endothelial VCAM-1, in contrast to ICAM-1, is

not

up-regulated by day 2 of nephrotoxic nephritis, and plays little part in early leukocyte influx into glomeruli. However, VLA-4 is an important mediator of glomerular injury, operating after transendothelial leukocyte migration, and presumably binding to alternate ligands within the kidney.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't

Albuminuria: IM, immunology

Albuminuria: PA, pathology

Albuminuria: TH, therapy

**Antibodies, Monoclonal: ME, metabolism**

\***Antibodies, Monoclonal: PD, pharmacology**

**Antibodies, Monoclonal: TU, therapeutic use**

**Apoptosis: IM, immunology**

Cell Movement: IM, immunology

Endothelium, Vascular: IM, immunology

\*Endothelium, Vascular: ME, metabolism

\*Glomerulonephritis: IM, immunology

\*Glomerulonephritis: ME, metabolism

Glomerulonephritis: PA, pathology

Glomerulonephritis: TH, therapy

Immunohistochemistry

\***Integrins: IM, immunology**

**Integrins: PH, physiology**

Iodine Radioisotopes: ME, metabolism

Kidney Glomerulus: IM, immunology

Kidney Glomerulus: ME, metabolism

\*Kidney Glomerulus: PA, pathology

**Leukocytes: PA, pathology**

Rats

Rats, Inbred WKY

\*Receptors, Lymphocyte Homing: IM, immunology

Receptors, Lymphocyte Homing: PH, physiology

\*Vascular Cell Adhesion Molecule-1: BI, biosynthesis

Vascular Cell Adhesion Molecule-1: IM, immunology

Vascular Cell Adhesion Molecule-1: PH, physiology

L17 ANSWER 6 OF 26 MEDLINE

AN 199218453 MEDLINE

DN 99218453

TI Ligation of Fc gamma RII (CD32) pivotally regulates survival of human eosinophils.

AU Kim J T; Schimming A W; Kita H

CS Department of Immunology, Mayo Clinic and Mayo Foundation, Rochester, MN 55905, USA.

NC AI 34486 (NIAID)

AI 34577 (NIAID)

SO JOURNAL OF IMMUNOLOGY, (1999 Apr 1) 162 (7) 4253-9.

Journal code: IFB. ISSN: 0022-1767.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199907  
EW 19990703  
AB The low-affinity IgG Fc receptor, FcgammaRII (CD32), mediates various effector functions of lymphoid and myeloid cells and is the major IgG Fc receptor expressed by human eosinophils. We investigated whether FcgammaRII regulates both cell survival and death of human eosinophils. When cultured in vitro without growth factors, most eosinophils undergo **apoptosis** within 96 h. Ligation of FcgammaRII by anti-CD32 mAb in solution inhibited eosinophil **apoptosis** and prolonged survival in the absence of growth factors. Cross-linking of human IgG bound to FcgammaRII by anti-human IgG Ab or of unoccupied FcgammaRII by aggregated human IgG also prolonged eosinophil survival. The enhanced survival with anti-CD32 mAb was inhibited by anti-granulocyte-macrophage-CSF (GM-CSF) mAb, suggesting that autocrine production of GM-CSF by eosinophils mediated survival. In fact, mRNA for GM-CSF was detected in eosinophils cultured with anti-CD32 mAb. In contrast to mAb or ligands in solution, anti-CD32 mAb or human IgG, when immobilized onto tissue culture plates, facilitated eosinophil cell death even in the presence of IL-5. Cell death induced by these immobilized ligands was accompanied by DNA fragmentation and was inhibited when eosinophil beta2 **integrin** was blocked by anti-CD18 mAb, suggesting that beta2 **integrins** play a key role in initiating eosinophil **apoptosis**. Thus, FcgammaRII may pivotally regulate both survival and death of eosinophils, depending on the manner of receptor ligation and beta2 **integrin** involvement. Moreover, the FcgammaRII could provide a novel mechanism to control the number of eosinophils at inflammation sites in human diseases.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.  
**Antibodies, Monoclonal: PD, pharmacology**  
Antigens, CD18: PH, physiology  
Autocrine Communication: IM, immunology  
Cell Death: IM, immunology  
Cell Survival: IM, immunology  
Cells, Cultured  
Cytokines: PH, physiology  
**Eosinophils: CY, cytology**  
**\*Eosinophils: IM, immunology**  
**\*Eosinophils: ME, metabolism**  
IgG: PD, pharmacology  
Ligands  
\*Receptors, IgG: IM, immunology  
\*Receptors, IgG: ME, metabolism  
Solubility

L17 ANSWER 7 OF 26 MEDLINE  
AN 1999167422 MEDLINE  
DN 99167422  
TI Laminin 5 promotes activation and **apoptosis** of the T cells expressing alpha3beta1 **integrin**.  
AU Sato K; Katagiri K; Hattori S; Tsuji T; Irimura T; Irie S; Katagiri T  
CS Research Institute of Biomatix, Nippi Co., Ltd., Tokyo, 120, Japan.  
SO EXPERIMENTAL CELL RESEARCH, (1999 Mar 15) 247 (2) 451-60.  
Journal code: EPB. ISSN: 0014-4827.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals

EM 199906  
 EW 19990603  
 AB By introducing an alpha3 gene-containing plasmid into a human T cell line Jurkat, we prepared the T cells, which express a high level of the alpha3beta1 **integrin**, to assess the role of laminin 5 in the skin immune system. The alpha3beta1-expressing T cells adhered to laminin 5 and exhibited spreading. These adhered T cells showed a significant tyrosine phosphorylation of intracellular proteins including p59(fyn) upon T-cell receptor (TCR) stimulation. Six hours after cross-linking TCR, these cells on laminin 5 secreted a three times higher level of IL-2 than those on a BSA-coated plate. Twenty hours after the stimulation, 48% of the alpha3beta1-expressing T cells on laminin 5 caused **apoptosis**. The protein level of cyclin D3 and E decreased, while that of p53 increased in these T cells. These data suggest that laminin 5 may play at least two regulatory roles for T cell functions: augmentation of IL-2 production by antigen-stimulated T cells and induction of **apoptosis** in these T cells. Copyright 1999 Academic Press.

CT Check Tags: Human; Support, Non-U.S. Gov't  
 \***Apoptosis**  
 Cell Adhesion  
 \*Cell Adhesion Molecules: ME, metabolism  
 Cell Movement  
 Cells, Cultured  
 Cyclins: BI, biosynthesis  
 Integrins: GE, genetics  
 \*Integrins: ME, metabolism  
 Interleukin-2: BI, biosynthesis  
 Jurkat Cells  
 Muromonab-CD3: ME, metabolism  
 Muromonab-CD3: PD, pharmacology  
 Phosphorylation  
 Protein p53: BI, biosynthesis  
 Receptors, Antigen, T-Cell: ME, metabolism  
 \***T-Lymphocytes: ME, metabolism**  
 Tyrosine: ME, metabolism

L17 ANSWER 8 OF 26 MEDLINE  
 AN 1999111422 MEDLINE  
 DN 99111422  
 TI Enhancement of activation-induced cell death by fibronectin in murine CD4+ CD8+ thymocytes.  
 AU Takayama E; Kina T; Katsura Y; Tadakuma T  
 CS Department of Parasitology, National Defense Medical College, Tokorozawa, Saitama 359, Japan.  
 SO IMMUNOLOGY, (1998 Dec) 95 (4) 553-8.  
 Journal code: GH7. ISSN: 0019-2805.  
 CY ENGLAND: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals  
 EM 199904  
 EW 19990402  
 AB Development of T cells in the thymus is achieved through the interactions of thymocytes with their microenvironments. This study focused on the function of fibronectin (FN), a major extracellular matrix molecule in the

thymus, in the cell death induced by activation via the T-cell antigen receptor. FN alone did not increase cell death in murine thymocytes above the baseline level, but it significantly enhanced the cell death induced by fixed anti-CD3 monoclonal antibody (mAb), especially when a high concentration of anti-CD3 mAb was used. DNA fragmentation increased in parallel with cell death, indicating that cell death was a result of the **apoptosis**. Fluorescence-activated cell sorter (FACS) analysis revealed that the activation-induced cell death (AICD) caused by anti-CD3 mAb alone, or by a combination of anti-CD3 mAb and FN, occurred selectively in CD4+ CD8+ thymocytes. Very late activation antigen (VLA)-4 and VLA-5 are two major ligands to FN on thymocytes. The expression of both ligands was investigated at different stages of thymocyte development. VLA-4 was predominantly expressed at the CD4- CD8- stage,

and

thereafter the expression was reduced, whereas VLA-5 was constantly expressed during maturation. Furthermore, the enhancing effect by FN was inhibited in the presence of the Gly-Arg-Gly-Asp-Ser-Pro (GRGDSP) peptide but not in the presence of the connecting segment-1 (CS-1) peptide, suggesting that enhancement of AICD observed in CD4+ CD8+ thymocytes is mediated through VLA-5.

CT

Check Tags: Animal  
 Anti-Allergic Agents  
**Antibodies, Monoclonal: PD, pharmacology**  
 Antigens, CD3: IM, immunology  
**\*Apoptosis: DE, drug effects**  
 Cells, Cultured  
**CD4-Positive T-Lymphocytes: PH, physiology**  
**CD8-Positive T-Lymphocytes: PH, physiology**  
 DNA Fragmentation  
 \*Fibronectins: PD, pharmacology  
 Flow Cytometry  
**Integrins: ME, metabolism**  
 \*Lymphocyte Transformation  
 Mice  
 Mice, Inbred BALB C  
 Oligopeptides: PD, pharmacology  
 Receptors, Antigen, T-Cell: ME, metabolism  
 Receptors, Fibronectin: ME, metabolism  
 Receptors, Lymphocyte Homing: ME, metabolism  
**\*T-Lymphocytes: PH, physiology**

L17 ANSWER 9 OF 26 MEDLINE

AN 1999097301 MEDLINE

DN 99097301

TI Prevention of experimental allergic encephalomyelitis by an antibody to CD45RB.

AU Schiffenbauer J; Butfiloski E; Hanley G; Sobel E S; Streit W J; Lazarovits

A

CS Department of Medicine, University of Florida College of Medicine, Gainesville, Florida, 32610, USA.

SO CELLULAR IMMUNOLOGY, (1998 Dec 15) 190 (2) 173-82.

Journal code: CQ9. ISSN: 0008-8749.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199904

AB CD45 is involved in the regulation of lymphocyte activation, and it has been demonstrated that ligation of CD45 induces **apoptosis** of T and B lymphocytes. Recently anti-CD45RB antibody therapy was shown to block acute allograft rejection in a mouse model of transplantation. Therefore, we wanted to examine the effects of anti-CD45RB antibody treatment on the course of an autoimmune disorder, experimental allergic encephalomyelitis (EAE), a Th1-mediated process. Mice immunized with myelin basic protein and treated with anti-CD45RB antibody did not develop

EAE. Histologically, there was no evidence of lymphocytic infiltrates in the central nervous system. T cell proliferation and TNF-alpha production were significantly decreased in anti-CD45RB-treated mice. Furthermore, there was a significant reduction in the production of other Th1

cytokines

including interferon-gamma and IL-2, but not IL-4 or IL-6. However, levels

of a number of adhesion markers or markers of activation such as VLA-4 and

LFA-1 on T cells were no different in treated versus control animals. Thus, anti-CD45RB can prevent EAE and appears to do so by altering T cell proliferation and cytokine production. Copyright 1998 Academic Press.

CT Check Tags: Animal; Support, Non-U.S. Gov't

**\*Antibodies, Monoclonal: TU, therapeutic use**

\*Antigens, CD45: IM, immunology

Cell Division

Cytokines: BI, biosynthesis

Encephalomyelitis, Experimental Autoimmune: IM, immunology

Encephalomyelitis, Experimental Autoimmune: PA, pathology

\*Encephalomyelitis, Experimental Autoimmune: PC, prevention & control

Encephalomyelitis, Experimental Autoimmune: TH, therapy

**Integrins: BI, biosynthesis**

Lymphocyte Function-Associated Antigen-1: BI, biosynthesis

Mice

Rats

Receptors, Lymphocyte Homing: BI, biosynthesis

**T-Lymphocytes: IM, immunology**

L17 ANSWER 10 OF 26 MEDLINE

AN 1999039370 MEDLINE

DN 99039370

TI Regulation of macrophage phagocytosis of apoptotic neutrophils by adhesion

to fibronectin.

AU McCutcheon J C; Hart S P; Canning M; Ross K; Humphries M J; Dransfield I

CS Rayne Laboratory, Edinburgh University Medical School, United Kingdom.

SO JOURNAL OF LEUKOCYTE BIOLOGY, (1998 Nov) 64 (5) 600-7.

Journal code: IYW. ISSN: 0741-5400.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199902

EW 19990204

AB The potential for leukocyte-mediated host tissue damage during resolution of inflammatory responses is influenced by the rate at which extravasated apoptotic leukocytes are cleared from inflammatory sites. Regulation of

macrophage capacity for clearance of apoptotic granulocytes is likely to be an important factor determining whether inflammation ultimately resolves or progresses to a chronic state. In this study we have investigated the molecular basis for rapid augmentation of macrophage phagocytosis of apoptotic neutrophils, which was observed following macrophage adhesion to fibronectin. We used a combination of monoclonal antibodies, blocking peptides, and recombinant fibronectin fragments to investigate the role of beta1 **integrins** in mediating the fibronectin effects. Blockade of alpha5beta1 or alpha4beta1 alone did not attenuate fibronectin-augmentation of phagocytosis. In addition, adhesion of macrophages to recombinant fibronectins lacking alpha4beta1 recognition motifs failed to promote phagocytosis of apoptotic neutrophils. Our results would be consistent with a model in which multiple fibronectin receptors, including beta1 **integrins**, act co-operatively to augment macrophage phagocytic responses. Together, these data suggest that the extracellular matrix environment of macrophages may provide regulatory signals that act indirectly to rapidly alter the potential for removal of apoptotic cells and influence the process of resolution of inflammation.

CT Check Tags: Human; Support, Non-U.S. Gov't  
 Antibodies, Blocking: PD, pharmacology  
**Antibodies, Monoclonal: PD, pharmacology**  
**\*Apoptosis**  
 Cell Adhesion  
 Extracellular Matrix: PH, physiology  
**\*Fibronectins: ME, metabolism**  
 Inflammation  
**Integrins: AI, antagonists & inhibitors**  
**Integrins: IM, immunology**  
**Integrins: PH, physiology**  
**\*Macrophages: PH, physiology**  
 Models, Biological  
**\*Neutrophils: CY, cytology**  
 Peptide Fragments: ME, metabolism  
 Peptide Fragments: PD, pharmacology  
**\*Phagocytosis**  
 Receptors, Fibronectin: AI, antagonists & inhibitors  
 Receptors, Fibronectin: IM, immunology  
 Receptors, Fibronectin: PH, physiology  
 Receptors, Lymphocyte Homing: AI, antagonists & inhibitors  
 Receptors, Lymphocyte Homing: IM, immunology  
 Receptors, Lymphocyte Homing: PH, physiology  
 Recombinant Proteins: ME, metabolism  
 Signal Transduction  
 Vitronectin: ME, metabolism

L17 ANSWER 11 OF 26 MEDLINE

AN 1999010946 MEDLINE

DN 99010946

TI Co-ligation of alpha4beta1 **integrin** and TCR rescues human thymocytes from steroid-induced **apoptosis**.

AU Zaitseva M B; Mojciak C F; Salomon D R; Shevach E M; Golding H

CS Division of Viral Products, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD 20892, USA.

SO INTERNATIONAL IMMUNOLOGY, (1998 Oct) 10 (10) 1551-61.

Journal code: AY5. ISSN: 0953-8178.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199904

EW 19990401

AB Maturation of thymocytes represents a sequence of events during which thymocytes expressing TCR with moderate avidity for self antigen/MHC are positively selected, whereas those with high or insufficient TCR avidity die. Glucocorticoids are produced intrathymically and can contribute to **apoptosis** of unselected thymocytes. Thymocytes differentiate in a close contact with epithelial cells, expressing vascular adhesion molecule-1 (VCAM-1) and secreting glucocorticoids, with bone marrow-derived macrophages, and with extracellular matrix containing fibronectin (FN) and collagen. Their contact with FN is mediated by alpha4beta1 and alpha5beta1 **integrins**. We examined the contribution of TCR and **integrin** signaling to the survival of thymocytes from dexamethasone (Dex)-induced **apoptosis**. We demonstrate that FN and VCAM-1 (both of which bind alpha4beta1 **integrin**), but not collagen, considerably augment TCR-mediated protection of thymocytes from Dex-induced **apoptosis**. This 'survival' signal is transduced through the alphabeta1, but not through the alpha5beta1 **integrin**. The observed protection from Dex-induced **apoptosis** correlated with an increase in bcl-2 protein levels. FN-alpha4beta1 and VCAM-1-alpha4beta1 engagement induced up-regulation bcl-2 protein, while alpha5beta1 binding to FN induced a negative signal that was blocked by anti-alpha5beta1 antibody. These data suggest that alpha4beta1 **integrin** may contribute to protection of thymocytes with moderate avidity TCR from glucocorticoid-induced death during intrathymic maturation.

CT Check Tags: Human

**Antibodies, Monoclonal: PD, pharmacology**

**Apoptosis: DE, drug effects**

Child, Preschool

\*Dexamethasone: PD, pharmacology

Fibronectins: PD, pharmacology

Infant

\***Integrins: ME, metabolism**

**Integrins: PH, physiology**

Ionomycin: PD, pharmacology

Proto-Oncogene Proteins c-bcl-2: BI, biosynthesis

Receptors, Antigen, T-Cell: IM, immunology

\*Receptors, Antigen, T-Cell: ME, metabolism

Receptors, Fibronectin: PH, physiology

\*Receptors, Lymphocyte Homing: ME, metabolism

Receptors, Lymphocyte Homing: PH, physiology

Recombinant Proteins: PD, pharmacology

Signal Transduction: PH, physiology

**T-Lymphocytes: DE, drug effects**

**T-Lymphocytes: ME, metabolism**

\***T-Lymphocytes: PH, physiology**

Tetradecanoylphorbol Acetate: PD, pharmacology

Vascular Cell Adhesion Molecule-1: PD, pharmacology

L17 ANSWER 12 OF 26 MEDLINE

AN 1999007959 MEDLINE

DN 99007959  
 TI Adhesion molecules in clinical medicine.  
 AU Cavenagh J D; Cahill M R; Kelsey S M  
 CS Dept. of Haematology, Royal London Hospital, UK.  
 SO CRITICAL REVIEWS IN CLINICAL LABORATORY SCIENCES, (1998 Sep) 35 (5)  
 415-59. Ref: 237  
 Journal code: AFY. ISSN: 1040-8363.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 199902  
 EW 19990204  
 AB Cellular adhesion molecules (CAMs) are critical components in the  
 processes of embryogenesis, tissue repair and organization, lymphocyte  
 function, lymphocyte homing and tumor metastasis, as well as being  
 central  
 to the interactions between hemopoietic progenitors and bone marrow  
 microenvironment, and between leukocytes and platelets with vascular  
 endothelium. Expression of CAMs regulates normal hemopoiesis and  
 migration  
 and function of mature hemopoietic cells. CAMs are an important part of  
 the inflammatory response and may regulate cytokine synthesis. In  
 addition, CAM expression may be critical for tumorigenesis. Monoclonal  
 antibodies to CAMs have been developed for clinical use; initial results  
 suggest that these agents have great potential in the prevention and  
 treatment of inflammation, thrombosis, reperfusion injury, and graft  
 rejection.  
 CT Check Tags: Human  
**Antibodies, Monoclonal: IM, immunology**  
**Apoptosis**  
 Blood Platelets: PH, physiology  
 Cadherins: CH, chemistry  
 Cell Adhesion Molecules: CH, chemistry  
 Cell Adhesion Molecules: IM, immunology  
 \*Cell Adhesion Molecules: ME, metabolism  
 \*Endothelium, Vascular: PH, physiology  
 Hematopoiesis  
 Immunoglobulins: CH, chemistry  
**Integrins: CH, chemistry**  
**\*Leukocytes: PH, physiology**  
 Proteoglycans: CH, chemistry  
 Selectins: CH, chemistry  
 L17 ANSWER 13 OF 26 MEDLINE  
 AN 1998241439 MEDLINE  
 DN 98241439  
 TI Mutation of CD95 (Fas/Apo-1) gene in adult T-cell leukemia cells.  
 AU Tamiya S; Etoh K; Suzushima H; Takatsuki K; Matsuoka M  
 CS The Second Department of Internal Medicine, Kumamoto University School of  
 Medicine, Kumamoto, Japan.  
 SO BLOOD, (1998 May 15) 91 (10) 3935-42.  
 Journal code: A8G. ISSN: 0006-4971.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)

LA English  
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
 EM 199808  
 EW 19980803  
 AB CD95 antigen (also known as Fas or Apo-1) and Fas ligand play key roles  
 in

**apoptosis** of cells of the immune system, function as effector molecules of cytotoxic T lymphocytes, and function in the elimination of activated lymphocytes during the downregulation of the immune response. The critical roles of the Fas-Fas ligand system in **apoptosis** suggest that its inactivation may be involved in malignant transformation.

We analyzed the expression of Fas antigen on adult T-cell leukemia (ATL) cells by flow cytometry and found that Fas antigen expression was absent in a case of ATL and markedly decreased in another case among 47 cases examined. **Apoptosis** could not be induced in the Fas-negative ATL cells by antibody against Fas antigen. Sequencing of reverse transcription-polymerase chain reaction products of the Fas genes in the Fas negative cells showed two types of aberrant transcripts: one had a 5-bp deletion and a 1-bp insertion in exon 2, and the other transcript lacked exon 4. These mutations caused the premature termination of both alleles, resulting in the loss of expression of surface Fas antigen.

These aberrant transcripts were not detected in a nonleukemic B-cell line from the same patient. An RNase protection assay of the Fas gene showed mutations in 2 additional cases with Fas-positive ATL cells of 35 cases examined: 1 case lacked exon 4 and the other was a silent mutation. In

the Fas antigen-negative case, leukemic cells were resistant to anticancer drugs in vivo, indicating that the loss of expression of Fas antigen may be associated with a poor response to anticancer drugs. Indeed, Fas-negative ATL cells were resistant to adriamycin-induced **apoptosis** in vitro, which is consistent with the finding that ATL in this case was resistant to chemotherapy. These findings indicate that mutation of the Fas gene may be associated with the progression of ATL

and with resistance to anticancer drugs.

CT Check Tags: Case Report; Human; Male; Support, Non-U.S. Gov't

Adult

Aged

Alleles

**Antibodies, Monoclonal: IM, immunology**

**Antibodies, Monoclonal: PD, pharmacology**

\*Antigens, CD95: GE, genetics

Antigens, CD95: IM, immunology

Antineoplastic Agents: TU, therapeutic use

Antiviral Agents: TU, therapeutic use

**Apoptosis: GE, genetics**

Cyclophosphamide: AD, administration & dosage

Doxorubicin: AD, administration & dosage

Drug Resistance, Neoplasm: GE, genetics

DNA Mutational Analysis

DNA, Neoplasm: GE, genetics

Etoposide: AD, administration & dosage

Exons: GE, genetics

Fatal Outcome

\*Gene Expression Regulation, Leukemic

HTLV-I: IP, isolation & purification  
 Interferon-alpha: TU, therapeutic use  
**Leukemia-Lymphoma, T-Cell, Acute, HTLV-I-Associated: DT, drug therapy**  
 \*Leukemia-Lymphoma, T-Cell, Acute, HTLV-I-Associated: GE, genetics  
 \*Neoplasm Proteins: GE, genetics  
**Neutrophils: ME, metabolism**  
 Polymerase Chain Reaction  
 Prednisone: AD, administration & dosage  
 RNA, Messenger: GE, genetics  
 RNA, Neoplasm: GE, genetics  
 Sequence Deletion  
**T-Lymphocytes: ME, metabolism**  
 Tumor Stem Cells: ME, metabolism  
 Vincristine: AD, administration & dosage  
 Zidovudine: TU, therapeutic use

L17 ANSWER 14 OF 26 MEDLINE  
 AN 1998189224 MEDLINE  
 DN 98189224  
 TI Selective expression of beta 7 **integrin** on lymphocytes undergoing **apoptosis** in lymphoid tissues.  
 AU Akari H; Yagita H; Nishida T; Nakamaru K; Terao K; Yoshikawa Y; Adachi A  
 CS Department of Virology, School of Medicine, University of Tokushima, Japan.. akari@basic.med.tokushima-u.ac.jp  
 SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1998 Mar 17) 244 (2)  
 578-82.  
 Journal code: 9Y8. ISSN: 0006-291X.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals  
 EM 199806  
 EW 19980604  
 AB It has been previously shown that the beta 7 chain of **integrin** forms heterodimers with the alpha 4 or alpha E chain, which plays essential roles in lymphocyte homing to mucosal lymphoid tissues. The aim of this study was to re-evaluate the possible role of the beta 7 **integrin** other than lymphocyte homing. We prepared spleen and lymph node lymphocytes from biopsied specimens from macaque monkeys and examined for the reactivity with a monoclonal antibody specific for the beta 7 chain. As a result, a minor population of the lymphocytes with a smaller size, which were in the early stage of **apoptosis**, was found to express a higher level of the beta 7 **integrin** than a majority of the lymphocytes with a normal size. Interestingly, the apoptotic lymphocytes expressed neither alpha 4 nor alpha E chains, suggesting that the beta 7 chain on these cells may be associated with an undefined alpha chain. These findings indicate that in the lymphoid tissues the shrunken lymphocytes undergoing **apoptosis** selectively express a unique beta 7 **integrin**.  
 CT Check Tags: Animal; Human  
**Antibodies, Monoclonal**  
 \*Apoptosis: IM, immunology  
 Cell Line  
 Cell Size  
 \*Integrins: ME, metabolism

Lymph Nodes: CY, cytology  
 Lymph Nodes: IM, immunology  
 \*Lymphocytes: CY, cytology  
 \*Lymphocytes: IM, immunology  
 \*Lymphoid Tissue: CY, cytology  
 \*Lymphoid Tissue: IM, immunology  
 Macaca  
 Spleen: CY, cytology  
 Spleen: IM, immunology

L17 ANSWER 15 OF 26 MEDLINE

AN 1998033176 MEDLINE

DN 98033176

TI Beta2 **integrins** (CD11/CD18) promote **apoptosis** of human neutrophils.

AU Walzog B; Jeblonski F; Zakrzewicz A; Gaehtgens P

CS Department of Physiology, Freie Universitat, Berlin, Germany.

SO FASEB JOURNAL, (1997 Nov) 11 (13) 1177-86.

Journal code: FAS. ISSN: 0892-6638.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199802

EW 19980204

AB **Apoptosis** of human polymorphonuclear neutrophils (PMN) is thought to be critical for the control of the inflammatory process, but the mechanisms underlying its regulation in physiological settings are still incompletely understood. This study was undertaken to test the hypothesis that the beta2 **integrin** (CD11/CD18) family of leukocyte adhesion molecules contributes to the control of activated PMN by up-regulating **apoptosis**. **Apoptosis** of isolated human PMN was investigated by 1) analysis of DNA content, 2) detection of DNA degradation, 3) morphological studies, and 4) measurement of CD16 expression on the cell surface. We found that beta2 **integrins** potentiated the tumor necrosis factor alpha (TNF-alpha) -induced **apoptosis** within 4 and 8 h after stimulation. The effect required aggregation of the beta2 **integrin** Mac-1 (CD11b/CD18), which was induced by antibody cross-linking, and was independent of Fc receptors.

An enhancement of **apoptosis** was also observed after migration of PMN through an endothelial cell monolayer. TNF-alpha-induced **apoptosis** as well as potentiation by beta2 **integrins** was prevented by inhibition of tyrosine kinases with herbimycin A or genistein. The present study provides a new model for the regulation of PMN **apoptosis** by a functional cross-talk between beta2 **integrins** and TNF-alpha with a promoting role for the beta2 **integrins**. This mechanism, which allows enhanced elimination of previously emigrated PMN, may be critical to abate local inflammatory processes in vivo.

CT Check Tags: Human; In Vitro; Support, Non-U.S. Gov't

**Antibodies, Monoclonal: PD, pharmacology**

Antigens, CD: BI, biosynthesis

Antigens, CD: PH, physiology

Antigens, CD18: IM, immunology

\*Antigens, CD18: PH, physiology

\***Apoptosis**

Cell Line  
 Chemotaxis, Leukocyte: DE, drug effects  
 Chemotaxis, Leukocyte: PH, physiology  
 Cross-Linking Reagents  
 DNA: BL, blood  
 DNA Fragmentation  
 Endothelium, Vascular: PH, physiology  
 Intercellular Adhesion Molecule-1: BI, biosynthesis  
 Kinetics  
 Macrophage-1 Antigen: IM, immunology  
 \*Macrophage-1 Antigen: PH, physiology  
 N-Formylmethionine Leucyl-Phenylalanine: PD, pharmacology  
**Neutrophils: CY, cytology**  
**Neutrophils: DE, drug effects**  
**\*Neutrophils: PH, physiology**  
 Receptors, IgG: BI, biosynthesis  
 Time Factors  
 Tumor Necrosis Factor: PD, pharmacology

L17 ANSWER 16 OF 26 MEDLINE

AN 97419184 MEDLINE

DN 97419184

TI High levels of a major histocompatibility complex II-self peptide complex on dendritic cells from the T cell areas of lymph nodes.

AU Inaba K; Pack M; Inaba M; Sakuta H; Isdell F; Steinman R M

CS Kyoto University, Kitashirakawa-Oiusake-cho, Kyoto 606-01, Japan.

NC AI-13013 (NIAID)

DK-39672 (NIDDK)

SO JOURNAL OF EXPERIMENTAL MEDICINE, (1997 Aug 29) 186 (5) 665-72.

Journal code: I2V. ISSN: 0022-1007.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199712

EW 19971201

AB T lymphocytes recirculate continually through the T cell areas of peripheral lymph nodes. During each passage, the T cells survey the surface of large dendritic cells (DCs), also known as interdigitating cells. However, these DCs have been difficult to release from the lymph node. By emphasizing the use of calcium-free media, as shown by Vremec et al. (Vremec, D., M. Zorbas, R. Scollay, D.J. Saunders, C.F. Ardavin, L. Wu, and K. Shortman. 1992. J. Exp. Med. 176:47-58.), we have been able to release and enrich DCs from the T cell areas. The DCs express the CD11c leukocyte **integrin**, the DEC-205 multilectin receptor for antigen presentation, the intracellular granule antigens which are recognized by monoclonal antibodies M342, 2A1, and MIDC-8, very high levels of MHC I

and

MHC II, and abundant accessory molecules such as CD40, CD54, and CD86. When examined with the Y-Ae monoclonal which recognizes complexes formed between I-Ab and a peptide derived from I-Ealpha, the T cell area DCs expressed the highest levels. The enriched DCs also stimulated a T-T hybridoma specific for this MHC II-peptide complex, and the hybridoma underwent **apoptosis**. Therefore DCs within the T cell areas can be isolated. Because they present very high levels of self peptides,

these

DCs should be considered in the regulation of self reactivity in the

periphery.  
 CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.  
**Antibodies, Monoclonal: IM, immunology**  
 Antigen Presentation  
 Antigen-Presenting Cells: IM, immunology  
 Antigens, CD: AN, analysis  
 Bone Marrow: IM, immunology  
 Dendritic Cells: CH, chemistry  
 \*Dendritic Cells: IM, immunology  
 Epidermis: IM, immunology  
 Flow Cytometry  
 \*Histocompatibility Antigens Class II: IM, immunology  
 Histocompatibility Antigens Class II: ME, metabolism  
 Hybridomas: IM, immunology  
 Immunohistochemistry  
 Interleukin-2: SE, secretion  
 Lymph Nodes: CY, cytology  
 \*Lymph Nodes: IM, immunology  
 Mice  
 Mice, Inbred C57BL  
 Mice, Inbred DBA  
**\*T-Lymphocytes: IM, immunology**

L17 ANSWER 17 OF 26 MEDLINE

AN 97220203 MEDLINE

DN 97220203

TI TGF-beta inhibits growth and induces **apoptosis** in leukemic B cell precursors.

AU Buske C; Becker D; Feuring-Buske M; Hannig H; Wulf G; Schafer C; Hiddemann W; Wormann B

CS Department of Hematology/Oncology, University of Gottingen, Germany.

SO LEUKEMIA, (1997 Mar) 11 (3) 386-92.  
 Journal code: LEU. ISSN: 0887-6924.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199706

EW 19970602

AB The uncontrolled proliferation of malignant lymphoblasts is the pathobiological hallmark in B cell precursor-ALL (BCP-ALL).

Identification

of inhibitory growth factors is of great importance for the understanding of growth control of leukemic B cell precursors and the development of novel therapeutic approaches in BCP-ALL. The aim of our study was the analysis of the effect of TGF-beta on cell survival and **apoptosis** of B cell precursors (BCP) from patients with acute lymphoblastic leukemia

in vitro. Experiments were performed in a coculture system with cloned murine fibroblasts, which efficiently block spontaneous ex vivo **apoptosis** of BCP and thus allows the assessment of cytokine-induced growth inhibition. TGF-beta significantly reduced cell viability of highly purified, FACS isolated CD10+/CD19+ leukemic BCP by a mean of 53% (P = 0.0001). The loss of cell viability was accompanied by a significant increase of **apoptosis** with a mean of 70% (P = 0.0028). The TGF-beta effect was blocked specifically by a monoclonal

anti-TGF-beta antibody. Induction of apoptotic cell death by TGF-beta was not accompanied by reduction of bcl-2 protein expression. TGF-beta transcription was not detected in the leukemic pre-B cell line BLIN-1, but in the murine fibroblasts. The growth inhibitory effect of TGF-beta was not restricted to leukemic BCP. The cytokine also increased **apoptosis** of normal, highly purified BCP by a mean of 58%. The data identify TGF-beta as a potent growth inhibitory cytokine for leukemic BCP.

CT Check Tags: Animal; Human  
**Antibodies, Monoclonal: PD, pharmacology**  
**\*Apoptosis: DE, drug effects**  
**B-Lymphocytes: CY, cytology**  
**B-Lymphocytes: DE, drug effects**  
**B-Lymphocytes: ME, metabolism**  
 Cell Division: DE, drug effects  
 Cell Survival: DE, drug effects  
 Cells, Cultured  
 Hematopoietic Stem Cells: CY, cytology  
 Hematopoietic Stem Cells: DE, drug effects  
 Hematopoietic Stem Cells: ME, metabolism  
 Interleukin-7: PD, pharmacology  
**Leukemia, Lymphocytic, Acute: DT, drug therapy**  
 Leukemia, Lymphocytic, Acute: ME, metabolism  
**\*Leukemia, Lymphocytic, Acute: PA, pathology**  
**\*Leukemia, Pre-B-Cell: DT, drug therapy**  
 Leukemia, Pre-B-Cell: ME, metabolism  
**\*Leukemia, Pre-B-Cell: PA, pathology**  
 Mice  
 Proto-Oncogene Proteins c-bcl-2: BI, biosynthesis  
 Transforming Growth Factor beta: BI, biosynthesis  
 Transforming Growth Factor beta: IM, immunology  
**\*Transforming Growth Factor beta: PD, pharmacology**

L17 ANSWER 18 OF 26 MEDLINE

AN 97211871 MEDLINE

DN 97211871

TI The **integrin**-triggered rescue of T lymphocyte **apoptosis** is blocked in HIV-1-infected individuals.

AU Ng T T; Kanner S B; Humphries M J; Wickremasinghe R G; Nye K E; Anderson J; Khoo S H; Morrow W J

CS Department of Immunology, St. Bartholomew's and Royal London School of Medicine and Dentistry, United Kingdom.

SO JOURNAL OF IMMUNOLOGY, (1997 Mar 15) 158 (6) 2984-99.  
 Journal code: IFB. ISSN: 0022-1767.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199706

EW 19970601

AB HIV infection is associated with a disease status-dependent impairment of Ag-specific T cell responses, resulting in anergy or unchecked apoptotic cell death. beta1 **integrins** play an important role in the induction of T lymphocyte responses to antigenic challenge by providing a T cell costimulatory signal, and have been shown to rescue various cell

types from undergoing **apoptosis**. We examined the **integrin**-triggered cell survival signal and associated pathways in CD3+ T cells derived from 69 HIV-1-infected individuals in comparison with healthy controls. We found beta1 **integrin**-mediated costimulation of TCR-induced T cell proliferation and protection from aberrant cell death to be absent in the majority of patients with AIDS, but intact in asymptomatic, infected individuals. The lack of **integrin**-mediated rescue may be partly due to an early impairment of TCR/**integrin**-costimulated secretion of IFN-gamma, a type 1 lymphokine that protects against TCR-induced **apoptosis** of T cells from HIV-seropositive donors, but not loss of **integrin** expression. The mechanism of **integrin** hyporesponsiveness appeared to correlate with a failure of the **integrin**-generated signal to induce ppl25FAK mRNA and protein expression. Protein kinase C activation in CD3+ T cells following **integrin** stimulation was also impaired in HIV-infected individuals, mostly among the symptomatic/AIDS patients. Protein kinase C inactivation in T cells was shown to have a destabilizing effect in vitro on ppl25FAK mRNA that contains an AUUUA motif in the 3'-untranslated region, a consensus sequence for the AU-rich elements responsible for mRNA destabilization. These aberrant changes in ppl25FAK expression may have direct significance to the overall immunopathogenesis during infection with HIV-1.

CT Check Tags: Human; Support, Non-U.S. Gov't  
 Acquired Immunodeficiency Syndrome: IM, immunology  
 Anti-HIV Agents: TU, therapeutic use  
**Antibodies, Monoclonal: PD, pharmacology**  
 Antigens, CD29: BI, biosynthesis  
**Apoptosis: DE, drug effects**  
**\*Apoptosis: IM, immunology**  
 Cell Adhesion Molecules: BI, biosynthesis  
 Cell Adhesion Molecules: BL, blood  
 Cell Adhesion Molecules: GE, genetics  
**CD4-Positive T-Lymphocytes: IM, immunology**  
 Drug Synergism  
 Enzyme Activation: DE, drug effects  
 Epitopes: PH, physiology  
 HIV Infections: DT, drug therapy  
**\*HIV Infections: IM, immunology**  
 HIV Infections: ME, metabolism  
 Immune Tolerance  
**Integrins: ME, metabolism**  
**\*Integrins: PH, physiology**  
 Interferon Type II: SE, secretion  
 Interphase  
**Leukemia, Lymphocytic**  
 Lymphocyte Transformation: DE, drug effects  
 Protein Kinase C: DE, drug effects  
 Protein-Tyrosine Kinase: BI, biosynthesis  
 Protein-Tyrosine Kinase: BL, blood  
 Protein-Tyrosine Kinase: GE, genetics  
 Receptor-CD3 Complex, Antigen, T-Cell: AI, antagonists & inhibitors  
 Receptor-CD3 Complex, Antigen, T-Cell: BI, biosynthesis  
 Receptor-CD3 Complex, Antigen, T-Cell: PH, physiology  
 RNA, Messenger: BI, biosynthesis  
 Signal Transduction: DE, drug effects

Signal Transduction: IM, immunology  
**T-Lymphocytes: DE, drug effects**  
**\*T-Lymphocytes: IM, immunology**  
 Tumor Cells, Cultured

L17 ANSWER 19 OF 26 MEDLINE  
 AN 97146068 MEDLINE  
 DN 97146068  
 TI Neutrophil **apoptosis** is modulated by endothelial transmigration and adhesion molecule engagement.  
 AU Watson R W; Rotstein O D; Nathens A B; Parodo J; Marshall J C  
 CS Department of Surgery, The Toronto Hospital, University of Toronto, Canada.  
 SO JOURNAL OF IMMUNOLOGY, (1997 Jan 15) 158 (2) 945-53.  
 Journal code: IFB. ISSN: 0022-1767.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
 EM 199704  
 EW 19970403  
 AB Termination of a neutrophil-mediated inflammatory response occurs through the activation of the endogenous cell death program, **apoptosis**. Neutrophil **apoptosis** is a constitutive process that can be accelerated or delayed by signals from the microenvironment. Since cellular localization at the site of an inflammatory challenge is the critical first step in a neutrophil response, we investigated the effects of neutrophil transendothelial transmigration on the kinetic expression of **apoptosis**. Neutrophils isolated from rat lung following challenge with LPS demonstrated a significant delay in spontaneous **apoptosis**. This delay was a consequence of transmigration, since a comparable delay was seen when TNF-alpha, a potent inducer of **apoptosis** in vitro, was used as the inflammatory stimulus. Human neutrophils demonstrated comparable delays in **apoptosis** in vitro following migration across an endothelial monolayer in response to FMLP. Delayed **apoptosis** only occurred in cells that had first been primed by LPS, a stimulus shown to up-regulate beta2 **integrins** and down-regulate L-selectin. Finally, crosslinking of CD11a or CD11b, but not of CD18, with mAbs and F(ab')2 fragments produced a delay in spontaneous **apoptosis**, whereas crosslinking of L-selectin with mAb or its natural ligand, sulfatides, accelerated the apoptotic process. Cells in which **apoptosis** was inhibited demonstrated persistent functional respiratory burst activity. These observations establish a role for endothelial transmigration in the regulation of neutrophil **apoptosis**, and suggest that adhesion molecules serve a modulatory role in the expression of neutrophil programmed cell death.  
 CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't  
**Antibodies, Monoclonal: IM, immunology**  
**Antibodies, Monoclonal: ME, metabolism**  
 Antigens, CD18: IM, immunology  
 Antigens, CD18: ME, metabolism  
**\*Apoptosis: DE, drug effects**  
 Bronchoalveolar Lavage Fluid: CY, cytology  
 Cell Adhesion Molecules: ME, metabolism

\*Cell Adhesion Molecules: PD, pharmacology  
 \*Cell Movement: PH, physiology  
 Endothelium, Vascular: ME, metabolism  
 L-Selectin: IM, immunology  
 L-Selectin: ME, metabolism  
 Lipopolysaccharides: PD, pharmacology  
 \*Neutrophils: DE, drug effects  
 \*Neutrophils: ME, metabolism  
 Protein Binding: IM, immunology  
 Rats  
 Rats, Sprague-Dawley  
 Tumor Necrosis Factor: PD, pharmacology

L17 ANSWER 20 OF 26 MEDLINE  
 AN 97066958 MEDLINE  
 DN 97066958  
 TI Characterization of a CD43/leukosialin-mediated pathway for inducing  
**apoptosis** in human T-lymphoblastoid cells.  
 AU Brown T J; Shuford W W; Wang W C; Nadler S G; Bailey T S; Marquardt H;  
 Mittler R S  
 CS Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle,  
 Washington 98121, USA.  
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Nov 1) 271 (44) 27686-95.  
 Journal code: HIV. ISSN: 0021-9258.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals  
 EM 199702  
 EW 19970204  
 AB The monoclonal antibody (mAb) J393 induces **apoptosis** in Jurkat  
 T-cells. NH2-terminal amino acid sequence analysis identified the 140-kDa  
 surface antigen for mAb J393 as CD43/leukosialin, the major  
 sialoglycoprotein of leukocytes. While Jurkat cells co-expressed two  
 discrete cell-surface isoforms of CD43, recognized by mAb J393 and mAb  
 G10-2, respectively, only J393/CD43 signaled **apoptosis**.  
 J393/CD43 was found to be hyposialylated, bearing predominantly O-linked  
 monosaccharide glycans, whereas G10-2/CD43 bore complex sialylated tetra-  
 and hexasaccharide chains. Treatment with soluble, bivalent mAb J393  
 killed 25-50% of the cell population, while concomitant engagement of  
 either the CD3.TcR complex or the **integrins** CD18 and CD29  
 significantly potentiated this effect. Treatment of Jurkat cells with mAb  
 J393 induced tyrosine phosphorylation of specific protein substrates that  
 underwent hyperphosphorylation upon antigen receptor costimulation.  
 Tyrosine kinase inhibition by herbimycin A diminished J393/CD43-mediated  
**apoptosis**, whereas inhibition of phosphotyrosine phosphatase  
 activity by bis(maltolato)oxovanadium-IV enhanced cell death. Signal  
 transduction through tyrosine kinase activation may lead to altered gene  
 expression, as J393/CD43 ligation prompted decreases in the nuclear  
 localization of the transcriptional regulatory protein NF-kappaB and  
 proteins binding the interferon-inducible regulatory element. Since  
 peripheral blood T-lymphocytes express cryptic epitopes for mAb J393,  
 these findings demonstrate the existence of a tightly regulated  
 CD43-mediated pathway for inducing **apoptosis** in human T-cell  
 lineages.  
 CT Check Tags: Human  
 \*Antibodies, Monoclonal

Antigens, CD: BI, biosynthesis  
 Antigens, CD: CH, chemistry  
 \*Antigens, CD: PH, physiology  
 \*Apoptosis  
 Base Sequence  
 Binding Sites  
 Carbohydrate Conformation  
 Carbohydrate Sequence  
 Cell Nucleus: ME, metabolism  
 Chromatography, Affinity  
 Enzyme Inhibitors: PD, pharmacology  
 Epitopes: AN, analysis  
 Flow Cytometry  
 Glycopeptides: CH, chemistry  
 Glycopeptides: IP, isolation & purification  
 Jurkat Cells  
 Lymphocyte Transformation  
 Microscopy, Confocal  
 Molecular Sequence Data  
 NF-kappa B: ME, metabolism  
 Oligonucleotide Probes  
 Oligosaccharides: CH, chemistry  
 Phosphorylation  
 Protein-Tyrosine Kinase: AI, antagonists & inhibitors  
 Protein-Tyrosine Kinase: ME, metabolism  
 Protein-Tyrosine-Phosphatase: AI, antagonists & inhibitors  
 Protein-Tyrosine-Phosphatase: ME, metabolism  
 Pyrones: PD, pharmacology  
 Quinones: PD, pharmacology  
 Sialoglycoproteins: BI, biosynthesis  
 Sialoglycoproteins: CH, chemistry  
 \*Sialoglycoproteins: PH, physiology  
 T-Lymphocytes: CY, cytology  
 T-Lymphocytes: IM, immunology  
 \*T-Lymphocytes: PH, physiology  
 Transcription Factors: ME, metabolism  
 Vanadates: PD, pharmacology

L17 ANSWER 21 OF 26 MEDLINE  
 AN 96374104 MEDLINE  
 DN 96374104  
 TI Human monocyte-derived macrophage phagocytosis of senescent eosinophils undergoing **apoptosis**. Mediation by alpha v beta 3/CD36/thrombospondin recognition mechanism and lack of phlogistic response.  
 AU Stern M; Savill J; Haslett C  
 CS Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, United Kingdom.  
 SO AMERICAN JOURNAL OF PATHOLOGY, (1996 Sep) 149 (3) 911-21.  
 Journal code: 3RS. ISSN: 0002-9440.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
 EM 199612  
 AB Eosinophils may mediate tissue injury in a number of allergic diseases. Previously, we reported that eosinophils constitutively undergo

**apoptosis** (programmed cell death) in culture. As this led to phagocytosis of the intact senescent cell by macrophages, we proposed that

**apoptosis** represented an injury-limiting eosinophil disposal mechanism. Ingestion of apoptotic neutrophils by human monocyte-derived macrophages (M phi s) was found to be mediated by adhesive interactions between thrombospondin and the M phi alpha v beta 3 vitronectin receptor **integrin** and M phi CD36. As this failed to elicit a pro-inflammatory response from M phi s, we sought evidence that this specific, nonphlogistic clearance mechanism may operate in eosinophil disposal. In this study, we found that M phi ingestion of apoptotic eosinophils was specifically inhibited by monoclonal antibodies to M phi alpha v beta 3, CD36, and thrombospondin and by other inhibitors of this recognition mechanism including RGD peptide and amino sugars.

Furthermore,

not only did M phi ingestion of intact apoptotic eosinophils fail to stimulate release of the phlogistic eicosanoid thromboxane, but there was also a lack of increased release of the pro-inflammatory cytokine granulocyte/macrophage colony-stimulating factor. However, increased release of these mediators was observed when M phi s took up senescent post-apoptotic eosinophils that had been cultured long enough to lose plasma membrane integrity. The data indicate that the nonphlogistic alpha v beta 3/CD36/thrombospondin macrophage recognition mechanism is

available

for clearance of intact senescent eosinophils undergoing **apoptosis**. Furthermore, our findings suggest that, by contrast, phagocytosis of post-apoptotic eosinophils may elicit undesirable pro-inflammatory responses.

CT Check Tags: Human; Support, Non-U.S. Gov't

Amino Sugars: PD, pharmacology

**Antibodies, Monoclonal: PD, pharmacology**

Antigens, CD36: IM, immunology

**Apoptosis: DE, drug effects**

\***Apoptosis: PH, physiology**

\*Cell Adhesion Molecules: IM, immunology

Cell Adhesion Molecules: PD, pharmacology

Cell Aging: PH, physiology

**Eosinophils: DE, drug effects**

\***Eosinophils: PH, physiology**

Granulocyte-Macrophage Colony-Stimulating Factor: SE, secretion

Macrophages: DE, drug effects

\*Macrophages: PH, physiology

\*Membrane Glycoproteins: IM, immunology

Membrane Glycoproteins: PD, pharmacology

**Monocytes: PH, physiology**

Oligopeptides: PD, pharmacology

Phagocytosis: DE, drug effects

\*Phagocytosis: PH, physiology

Receptors, Vitronectin: IM, immunology

Signal Transduction

Thromboxane A2: SE, secretion

L17 ANSWER 22 OF 26 MEDLINE

AN 96355032 MEDLINE

DN 96355032

TI Pleiotropic effects of immobilized versus soluble recombinant HIV-1 Tat protein on CD3-mediated activation, induction of **apoptosis**, and

HIV-1 long terminal repeat transactivation in purified CD4+ T lymphocytes.

AU Zauli G; Gibellini D; Celeghini C; Mischiati C; Bassini A; La Placa M; Capitani S

CS Institute of Human Anatomy, University of Ferrara, Italy.

SO JOURNAL OF IMMUNOLOGY, (1996 Sep 1) 157 (5) 2216-24.  
Journal code: IFB. ISSN: 0022-1767.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199701

EW 19970104

AB CD3 mAb and HIV-1 Tat protein co-immobilized on plastic were able to induce a strong proliferation of resting human CD4 T cells, cultured in a serum-free chemically defined medium. Blocking studies performed with heparin or peptides containing the RGD sequence demonstrated that the heparin-binding basic domain of Tat plays a predominant role in CD4+ T cell activation. Moreover, the enhanced proliferative response of CD4+ T cells to immobilized Tat appeared to be mediated by alpha 5, beta 1, and alpha v subunits of surface **integrin** receptors. In contrast, soluble Tat showed a dose-dependent inhibitory activity on the proliferative response of resting CD4+ T cells stimulated by CD3 mAb co-immobilized with Tat or fibronectin, but not with CD28 mAb. In transient transfection assays performed with an HIV-1 long terminal repeat (LTR)-chloramphenicol acetyltransferase (CAT) plasmid CD3 mAb co-immobilized with Tat or fibronectin or CD28 mAb significantly stimulated CAT activity over the background. On the other hand, while immobilized Tat alone had no effects on LTR transactivation, soluble Tat was able to transactivate LTR-CAT in a dose-dependent manner. When CD4+ T cells activated by CD3 mAb co-immobilized with Tat were recovered, cultured for 7 days with 25 U/ml recombinant IL-2, and given an additional activation signal by recross-linking CD3 mAb, a marked increase of **apoptosis** was observed with respect to cells not subjected to CD3 mAb recross-linking. While co-immobilized Tat plus CD3 mAb did not show any significant effect on activation-induced cell death, high concentrations of soluble Tat synergized with immobilized CD3 mAb in the induction of **apoptosis**.

CT Check Tags: Comparative Study; Human; Support, Non-U.S. Gov't  
Adult  
**Antibodies, Monoclonal: PD, pharmacology**  
Antigens, CD3: IM, immunology  
\*Antigens, CD3: PH, physiology  
\***Apoptosis: DE, drug effects**  
Cell Separation  
Cells, Cultured  
Cross-Linking Reagents  
**CD4-Positive T-Lymphocytes: DE, drug effects**  
\***CD4-Positive T-Lymphocytes: IM, immunology**  
Gene Products, tat: CH, chemistry  
\*Gene Products, tat: PD, pharmacology  
Heparin: PD, pharmacology  
\*HIV-1: IM, immunology  
\*Lymphocyte Transformation: DE, drug effects  
Oligopeptides: PD, pharmacology

Receptors, Antigen, T-Cell: ME, metabolism  
 Recombinant Proteins: CH, chemistry  
 \*Recombinant Proteins: PD, pharmacology  
 \*Repetitive Sequences, Nucleic Acid: DE, drug effects  
 Solubility  
 \*Trans-Activation (Genetics): DE, drug effects

L17 ANSWER 23 OF 26 MEDLINE

AN 96173790 MEDLINE

DN 96173790

TI Up-regulation of VLA-5 expression during monocytic differentiation and  
 its

role in negative control of the survival of peripheral blood monocytes.

AU Terui Y; Furukawa Y; Sakai T; Kikuchi J; Sugahara H; Kanakura Y; Kitagawa  
 S; Miura Y

CS Institute of Hematology, Jichi Medical School, Tochigi, Japan.

SO JOURNAL OF IMMUNOLOGY, (1996 Mar 1) 156 (5) 1981-8.

Journal code: IFB. ISSN: 0022-1767.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals

EM 199606

AB Interaction between fibronectin (FN) and very late activation Ag-5  
 (VLA-5)

**integrin** was recently reported to be involved in **apoptosis**  
 of hematopoietic cells. In an effort to clarify the physiologic role of

FN

in the regulation of biologic behavior of terminally differentiated  
 hematopoietic cells, we have examined the change of VLA-5 expression  
 during myeloid cell differentiation and its effects on monocytes and  
 granulocytes. VLA-5 alpha mRNA was up-regulated during monocytic  
 differentiation, but not during granulocytic differentiation of HL-60  
 cells. Flow cytometric and immunocytochemical analysis revealed that  
 surface expression of VLA-5 was selectively increased upon monocytic  
 differentiation and that it was strongly positive on peripheral blood  
 monocytes. Susceptibility to FN-induced **apoptosis** was greatly  
 increased upon monocytic differentiation, and it was almost completely  
 abrogated by anti-VLA-5 Ab or RGD peptide. Similarly, FN could  
 significantly enhance **apoptosis** of normal monocytes but not of  
 granulocytes. Finally, we have shown that anti-FN Ab could suppress  
 spontaneous **apoptosis** of normal monocytes in culture and prolong  
 their survival. These results suggest that FN might play an important

role

in negative regulation of the survival of monocytes through its  
 interaction with VLA-5, which is selectively up-regulated during

monocytic

differentiation.

CT Check Tags: Human; Support, Non-U.S. Gov't

**Antibodies, Monoclonal: PD, pharmacology**

**Apoptosis: DE, drug effects**

**Apoptosis: IM, immunology**

Base Sequence

Cell Differentiation: IM, immunology

Cell Survival: IM, immunology

Fibronectins: AI, antagonists & inhibitors

Fibronectins: IM, immunology

Fibronectins: PD, pharmacology  
**Granulocytes: ME, metabolism**  
 Immune Tolerance  
**Leukemia, Promyelocytic, Acute: GE, genetics**  
**Leukemia, Promyelocytic, Acute: ME, metabolism**  
**Leukemia, Promyelocytic, Acute: PA, pathology**  
 Molecular Sequence Data  
**Monocytes: CY, cytology**  
**\*Monocytes: DE, drug effects**  
**Monocytes: ME, metabolism**  
 \*Receptors, Fibronectin: BI, biosynthesis  
 Receptors, Fibronectin: GE, genetics  
 Receptors, Fibronectin: PH, physiology  
 Tumor Cells, Cultured  
 \*Up-Regulation (Physiology): IM, immunology

L17 ANSWER 24 OF 26 MEDLINE  
 AN 96116877 MEDLINE  
 DN 96116877  
 TI CD19 antigen in leukemia and lymphoma diagnosis and immunotherapy.  
 AU Scheuermann R H; Racila E  
 CS Laboratory of Molecular Pathology, University of Texas Southwestern  
 Medical Center, Dallas 75235-9072, USA.  
 SO LEUKEMIA AND LYMPHOMA, (1995 Aug) 18 (5-6) 385-97. Ref: 94  
 Journal code: BNQ. ISSN: 1042-8194.  
 CY Switzerland  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, ACADEMIC)  
 LA English  
 FS Priority Journals  
 EM 199604  
 AB The CD19 antigen plays an important role in clinical oncology. In normal  
 cells, it is the most ubiquitously expressed protein in the B lymphocyte  
 lineage. CD19 expression is induced at the point of B lineage commitment  
 during the differentiation of the hematopoietic stem cell, and its  
 expression continues through preB and mature B cell differentiation until  
 it is finally down-regulated during terminal differentiation into plasma  
 cells. CD19 expression is maintained in B-lineage cells that have  
 undergone neoplastic transformation, and therefore CD19 is useful in  
 diagnosis of leukemias and lymphomas using monoclonal antibodies (mAbs)  
 and flow cytometry. Interestingly, CD19 is also expressed in a subset of  
 acute myelogenous leukemias (AMLs) indicating the close relationship  
 between the lymphoid and myeloid lineages. Because B lineage leukemias  
 and lymphomas rarely lose CD19 expression, and because it is not expressed in  
 the pluripotent stem cell, it has become the target for a variety of  
 immunotherapeutic agents, including immunotoxins. Treatment of  
 non-Hodgkin's lymphoma (NHL) and acute lymphocytic leukemia (ALL) with  
 anti-CD19 mAbs coupled to biological toxins has proven to be effective in  
 vitro and in animal models, and has shown some promising results in Phase  
 I clinical trials. Recently, the analysis of anti-CD19 effects on  
 lymphoma cell growth has highlighted a novel mechanism of immunotherapy.  
 Engagement of cell surface receptors like CD19 by mAbs can have anti-tumor effects  
 by

the activation of signal transduction pathways which control cell cycle progression and programmed cell death (**apoptosis**).

CT Check Tags: Human  
 src-Family Kinases: ME, metabolism  
**Antibodies, Monoclonal**  
 \*Antigens, CD19: ME, metabolism  
 Antigens, CD19: TU, therapeutic use  
 Antigens, Neoplasm: IM, immunology  
**\*B-Lymphocytes: IM, immunology**  
 Bone Marrow: CY, cytology  
 Bone Marrow Purging  
 Cell Cycle  
 Clinical Trials  
 Immunotherapy  
 \*Leukemia: DI, diagnosis  
**Leukemia: TH, therapy**  
 Lymphocyte Depletion  
 \*Lymphoma: DI, diagnosis  
 Lymphoma: TH, therapy  
 Prognosis  
 Signal Transduction

L17 ANSWER 25 OF 26 MEDLINE

AN 95045906 MEDLINE

DN 95045906

TI Recognition of apoptotic cells by human macrophages: inhibition by a monocyte/macrophage-specific monoclonal antibody.

AU Flora P K; Gregory C D

CS Department of Immunology, University of Birmingham Medical School, Edgbaston..

SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1994 Nov) 24 (11) 2625-32.

Journal code: EN5. ISSN: 0014-2980.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 199502

AB Cells undergoing death by **apoptosis** are rapidly engulfed by phagocytes in vivo, a highly efficient process which prevents leakage of potentially dangerous intracellular contents from dying cells to neighboring tissue. We have tested a panel of monoclonal antibodies (mAb) specifying a range of human monocyte/macrophage surface antigens for

their

capacity to inhibit the in vitro recognition of apoptotic cells by human peripheral blood monocyte-derived macrophages. The results identify the antigen defined by the 61D3 mAb, a widely-used marker of monocyte/macrophage lineage cells, as an important mediator of apoptotic cell recognition. In our system, apoptotic, but not viable, cells were recognized by the cultured macrophages and 61D3 was found to inhibit the recognition of all apoptotic cell types tested, including Ca<sup>2+</sup> ionophore-treated or growth factor-depleted B and T lymphocyte lines, tonsillar germinal center B cells, irradiated peripheral blood

lymphocytes

and senescing neutrophils. Furthermore, the apoptotic cell recognition pathway specified by 61D3 could be distinguished from that involving the macrophage alpha v beta 3 vitronectin receptor which has been shown previously to play an important role in the recognition of apoptotic

cells. These results provide further evidence that the mechanisms underlying rapid clearance of apoptotic cells involve multiple phagocyte receptors.

CT Check Tags: Animal; Human; Support, Non-U.S. Gov't

**\*Antibodies, Monoclonal: IM, immunology**

**\*Apoptosis**

Cells, Cultured

**Integrins: PH, physiology**

**Lymphocytes: PH, physiology**

**\*Macrophages: PH, physiology**

Mice

**\*Monocytes: PH, physiology**

**Neutrophils: PH, physiology**

Receptors, Cytoadhesin: PH, physiology

L17 ANSWER 26 OF 26 MEDLINE

AN 89317480 MEDLINE

DN 89317480

TI Monoclonal antibody-mediated tumor regression by induction of **apoptosis**.

AU Trauth B C; Klas C; Peters A M; Matzku S; Moller P; Falk W; Debatin K M; Krammer P H

CS Institute for Immunology and Genetics, German Cancer Research Center, Heidelberg.

SO SCIENCE, (1989 Jul 21) 245 (4915) 301-5.  
Journal code: UJ7. ISSN: 0036-8075.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 198910

AB To characterize cell surface molecules involved in control of growth of malignant lymphocytes, monoclonal antibodies were raised against the human

B lymphoblast cell line SKW6.4. One monoclonal antibody, anti-APO-1, reacted with a 52-kilodalton antigen (APO-1) on a set of activated human lymphocytes, on malignant human lymphocyte lines, and on some patient-derived leukemic cells. Nanogram quantities of anti-APO-1 completely blocked proliferation of cells bearing APO-1 in vitro in a manner characteristic of a process called programmed cell death or **apoptosis**. Cell death was preceded by changes in cell morphology and fragmentation of DNA. This process was distinct from antibody- and complement-dependent cell lysis and was mediated by the antibody alone. A single intravenous injection of anti-APO-1 into nu/nu mice carrying a xenotransplant of a human B cell tumor induced regression of this tumor within a few days. Histological thin sections of the regressing tumor showed that anti-APO-1 was able to induce **apoptosis** in vivo. Thus, induction of **apoptosis** as a consequence of a signal mediated through cell surface molecules like APO-1 may be a useful therapeutic approach in treatment of malignancy.

CT Check Tags: Animal; Human; Support, Non-U.S. Gov't

**\*Antibodies, Monoclonal: IM, immunology**

**Antibodies, Monoclonal: TU, therapeutic use**

Antigens, Neoplasm: IM, immunology

Autoradiography

**B-Lymphocytes: IM, immunology**

Burkitt Lymphoma: IM, immunology

Burkitt Lymphoma: TH, therapy  
Cell Survival  
Cells, Cultured  
Electrophoresis, Polyacrylamide Gel  
\*Leukemia, B-Cell: IM, immunology  
Leukemia, B-Cell: PA, pathology  
**Leukemia, B-Cell: TH, therapy**  
Mice  
Mice, Nude  
Precipitin Tests  
Remission Induction  
**T-Lymphocytes: IM, immunology**  
Tumor Cells, Cultured

Helms 09/508,251

=> d his

(FILE 'HCAPLUS' ENTERED AT 09:52:29 ON 18 JAN 2001)

DEL HIS Y

L1 181014 S LEUKOCYTE# OR LYMPHOCYT? OR MONOCYT? OR MYELOCYT? OR WHITE  
BL  
L2 31415 S APOPTOSIS  
L3 4742 S L1 AND L2  
L4 51002 S MONOCLONAL#  
L5 131 S L3 AND L4  
L6 13734 S INTEGRIN?  
L7 7 S L5 AND L6  
L8 12788 S IAP OR IAP/AB OR INTEGRIN?/AB  
L9 2 S L8 AND L5  
L10 45335 S LEUKEMIA  
L11 22 S L10 AND (L6 OR L8) AND L4  
L12 3 S L11 AND L2  
L13 50 S NUCLEAT? (3A) BLOOD (3A) CELL#  
L14 2 S L13 AND L2 AND L4  
L15 7 S L7 OR L9 OR L12 OR L14

FILE 'WPIDS' ENTERED AT 10:00:57 ON 18 JAN 2001

L16 2176 S APOPTOSIS OR CELL (3A) DEATH  
L17 9155 S MONOCLONAL?  
L18 593 S INTEGRIN# OR IAP  
L19 6 S L16 AND L17 AND L18  
L20 36379 S ANTIBOD?  
L21 25 S L16 AND L20 AND L18  
L22 19 S L21 NOT L19  
L23 128027 S BLOOD OR NUCLEAT? OR CANCER OR TUMOR# OR TUMOUR# OR  
LEUKEMIA  
L24 12 S L22 AND L23  
L25 18 S L19 OR L24

FILE 'USPATFULL' ENTERED AT 10:05:30 ON 18 JAN 2001

L26 315 S (APOPTOSIS OR CELL (3A) DEATH)/TI,AB,CLM  
L27 596 S (APOPTOSIS OR CELL (3A) DEATH)/TI,AB,CLM  
L28 14704 S ANTIBOD?/TI,AB,CLM  
L29 239 S (INTEGRIN? OR IAP)/AB, TI, CLM  
L30 7 S L27 AND L28 AND L29  
L31 6276 S (LEUKEMIA OR BLOOD CELL# OR LYMPHOCYT? OR MONOCYTE? OR  
MYELOC  
L32 18 S L27 AND L28 AND L31  
L33 9 S L32 AND (INTEGRIN# OR IAP#)  
L34 15 S L33 OR L30

FILE 'USPATFULL, WPIDS, HCAPLUS' ENTERED AT 10:08:36 ON 18 JAN 2001

L35 37 DUP REM L34 L25 L15 (3 DUPLICATES REMOVED)

=> d bib ab 1-37

L35 ANSWER 1 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
DUPLICATE

AN 2000-587428 [55] WPIDS  
DNC C2000-175236  
TI Single stranded Fv antibody fragment inducing **apoptosis** in nucleated blood cells having **integrin** associated protein for treatment of leukemia.  
DC B04 D16  
IN FUKUSHIMA, N; UNO, S  
PA (CHUS) CHUGAI SEIYAKU KK  
CYC 90  
PI WO 2000053634 A1 20000914 (200055)\* JA 73p  
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
OA PT SD SE SL SZ TZ UG ZW  
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES  
FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS  
LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL  
TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW  
AU 2000029409 A 20000928 (200067)  
ADT WO 2000053634 A1 WO 2000-JP1458 20000310; AU 2000029409 A AU 2000-29409 20000310  
FDT AU 2000029409 A Based on WO 200053634  
PRAI JP 1999-63557 19990310  
AB WO 200053634 A UPAB: 20001102  
NOVELTY - A polypeptide containing the variable region of the light chain of a **monoclonal** antibody is new, and induces **apoptosis** in nucleated blood cells having **integrin** associate protein ( **IAP** ).  
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:  
(1) DNA encoding the novel polypeptide;  
(2) animal or microbial cells expressing the DNA of (1); and  
(3) agents for the treatment of blood disorders which contain the polypeptide.  
ACTIVITY - Cytostatic.  
MECHANISM OF ACTION - The antibody induces **apoptosis** in nucleated blood cells.  
USE - The treatment of blood disorders such as leukemia (claimed).  
Dwg.0/12

L35 ANSWER 2 OF 37 USPATFULL  
AN 2000:138521 USPATFULL  
TI Modulation of IAPs for the treatment of proliferative diseases  
IN Korneluk, Robert G., Ontario, Canada  
MacKenzie, Alexander E., Ontario, Canada  
Liston, Peter, Ottawa, Canada  
Baird, Stephen, Ottawa, Canada  
Tsang, Benjamin K., Nepean, Canada  
Pratt, Christine, Ontario, Canada  
PA Apoptogen, Inc., Ottawa, Canada (non-U.S. corporation)  
PI US 6133437 20001017  
AI US 1997-800929 19970213 (8)  
DT Utility  
EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Epps, Janet  
LREP Clark & Elbing LLP; Bieker-Brady, Ph.D., Kristina  
CLMN Number of Claims: 8  
ECL Exemplary Claim: 1  
DRWN 37 Drawing Figure(s); 33 Drawing Page(s)  
LN.CNT 3251

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are diagnostic and prognostic kits for the detection and treatment of proliferative diseases such as ovarian cancer, breast cancer, and lymphoma. Also disclosed are cancer therapeutics utilizing **IAP** antisense nucleic acids **IAP** fragments, and **antibodies** which specifically bind **IAP** polypeptides.

L35 ANSWER 3 OF 37 USPATFULL

AN 2000:109594 USPATFULL

TI XAF genes and polypeptides: methods and reagents for modulating **apoptosis**

IN Korneluk, Robert G., Ottawa, Canada

Tamai, Katsuyuki, Nagano, Japan

Liston, Peter, Ottawa, Canada

MacKenzie, Alexander E., Ottawa, Canada

PA Apoptogen Inc., Ottawa, Canada (non-U.S. corporation)

PI US 6107088 20000822

AI US 1998-100391 19980619 (9)

PRAI US 1997-52402 19970714 (60)

US 1997-54491 19970801 (60)

US 1997-56338 19970818 (60)

DT Utility

EXNAM Primary Examiner: Guzo, David; Assistant Examiner: Shuman, Jon

LREP Clark & Elbing LLP; Bieker-Brady, Kristina

CLMN Number of Claims: 28

ECL Exemplary Claim: 1

DRWN 59 Drawing Figure(s); 51 Drawing Page(s)

LN.CNT 4426

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides novel XAF nucleic acid sequences. Also provided are XAF polypeptides, anti-XAF **antibodies**, and methods for modulating **apoptosis** and detecting compounds which modulate **apoptosis**.

L35 ANSWER 4 OF 37 USPATFULL

AN 2000:109547 USPATFULL

TI Detection and modulation of **IAPS** for the diagnosis and treatment of proliferative disease

IN Korneluk, Robert G., Ontario, Canada

MacKenzie, Alexander E., Ontario, Canada

Liston, Peter, Ottawa, Canada

Baird, Stephen, Ottawa, Canada

Tsang, Benjamin K., Nepean, Canada

Pratt, Christine, Ontario, Canada

PA Apoptogen, Inc., Ottawa, Canada (non-U.S. corporation)

PI US 6107041 20000822

AI US 1998-212971 19981216 (9)

RLI Division of Ser. No. US 1997-800929, filed on 13 Feb 1997

PRAI US 1996-30590 19961114 (60)

US 1996-17354 19960426 (60)

DT Utility

EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Epps, Janets

LREP Clark & Elbing LLP; Bieker-Brady, Kristina

CLMN Number of Claims: 27

ECL Exemplary Claim: 1

DRWN 42 Drawing Figure(s); 33 Drawing Page(s)

LN.CNT 3255

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are diagnostic and prognostic kits for the detection and treatment of proliferative diseases such as ovarian cancer, breast cancer, and lymphoma. Also disclosed are cancer therapeutics utilizing **IAP** antisense nucleic acids **IAP** fragments, and **antibodies** which specifically bind **IAP** polypeptides.

L35 ANSWER 5 OF 37 USPATFULL

AN 2000:50686 USPATFULL

TI Regulated **apoptosis**

IN Crabtree, Gerald R., Woodside, CA, United States  
Schreiber, Stuart L., Cambridge, MA, United States  
Spencer, David M., Los Altos, CA, United States  
Wandless, Thomas J., Cambridge, MA, United States  
Belshaw, Peter, Cambridge, MA, United States

PA Board of Trustees of Leland S. Stanford Jr. Univ., Stanford, CA, United States (U.S. corporation)  
President & Fellows of Harvard College, Cambridge, MA, United States (U.S. corporation)

PI US 6054436 20000425

AI US 1998-87811 19980529 (9)

RLI Continuation of Ser. No. US 1994-292597, filed on 18 Aug 1994, now patented, Pat. No. US 5834266 which is a continuation-in-part of Ser. No. US 1994-179143, filed on 7 Jan 1994, now abandoned which is a continuation-in-part of Ser. No. US 1993-93499, filed on 16 Jul 1993, now abandoned And a continuation-in-part of Ser. No. US 1994-196043, filed on 14 Feb 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-179748, filed on 7 Jan 1994, now abandoned which is a continuation-in-part of Ser. No. US 1993-92977, filed on 16 Jul 1993, now abandoned which is a continuation-in-part of Ser. No. US

1993-17931,  
filed on 12 Feb 1993, now abandoned

DT Utility

EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Schwartzman, Robert

LREP Berstein, David L.; Hausdorff, Sharon F.; Clauss, Isabelle M.

CLMN Number of Claims: 64

ECL Exemplary Claim: 1

DRWN 35 Drawing Figure(s); 34 Drawing Page(s)

LN.CNT 5061

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB We have developed a general procedure for the regulated (inducible) dimerization or oligomerization of intracellular proteins and disclose methods and materials for using that procedure to regulatably initiate cell-specific **apoptosis** (programmed **cell death**) in genetically engineered cells.

L35 ANSWER 6 OF 37 USPATFULL

AN 2000:41069 USPATFULL

TI 12 (S)--hete receptor blockers

IN Natarajan, Rama, Hacienda Heights, CA, United States  
Nadler, Jerry L., La Crescenta, CA, United States

PA City of Hope, Duarte, CA, United States (U.S. corporation)

PI US 6046224 20000404

AI US 1998-172138 19981014 (9)

PRAI US 1997-62335 19971015 (60)

DT Utility

EXNAM Primary Examiner: Reamer, James H.  
LREP Rothwell, Figg, Ernst & Kurz  
CLMN Number of Claims: 15  
ECL Exemplary Claim: 1  
DRWN 9 Drawing Figure(s); 9 Drawing Page(s)  
LN.CNT 617

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The 12-lipoxygenase product, 12(S)-HETE, mediates hyperproliferative and

hyperplastic responses seen in atherosclerosis, diabetes, Parkinson's disease, Alzheimer's, stroke-induced nerve damage and cancer. 12-HETE also mediates inflammation and **cell death** in some **cell** systems, particularly B-islet cells of the pancreas. The present invention involves amelioration of disease states mediated by 12(S)-HETE by blocking specific 12(S)-HETE receptors.

L35 ANSWER 7 OF 37 USPATFULL

AN 2000:1861 USPATFULL

TI Regulated transcription of targeted genes and other biological events  
IN Crabtree, Gerald R., Woodside, CA, United States

Schreiber, Stuart L., Cambridge, MA, United States

Spencer, David M., Los Altos, CA, United States

Wandless, Thomas J., Cambridge, MA, United States

Belshaw, Peter, Cambridge, MA, United States

PA Board of Trustees of Leland Stanford Jr. University, Stanford, CA,  
United States (U.S. corporation)

President and Fellows of Harvard College, Cambridge, MA, United States  
(U.S. corporation)

PI US 6011018 20000104

AI US 1998-87716 19980529 (9)

RLI Continuation of Ser. No. US 1995-388653, filed on 14 Feb 1995, now  
patented, Pat. No. US 5869337 which is a continuation-in-part of Ser.  
No. US 1994-196043, filed on 11 Feb 1994, now abandoned which is a  
continuation-in-part of Ser. No. US 1994-179748, filed on 7 Jan 1994,  
now abandoned which is a continuation-in-part of Ser. No. US

1993-92977,  
filed on 16 Jul 1993, now abandoned which is a continuation-in-part of  
Ser. No. US 1993-17931, filed on 12 Feb 1993, now abandoned And a  
continuation-in-part of Ser. No. US 1994-292597, filed on 18 Aug 1994,  
now patented, Pat. No. US 5834266 which is a continuation-in-part of  
Ser. No. US 1994-179143, filed on 7 Jan 1994, now abandoned which is a  
continuation-in-part of Ser. No. US 1993-93499, filed on 16 Jul 1993,  
now abandoned

DT Utility

EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Schwartzman,  
Robert

LREP Bernstein, David L.; Hausdorff, Sharon F.; Vincent, Matthew P.

CLMN Number of Claims: 70

ECL Exemplary Claim: 1

DRWN 36 Drawing Figure(s); 36 Drawing Page(s)

LN.CNT 4687

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Dimerization and oligomerization of proteins are general biological  
control mechanisms that contribute to the activation of cell membrane  
receptors, transcription factors, vesicle fusion proteins, and other  
classes of intra- and extracellular proteins. We have developed a  
general procedure for the regulated (inducible) dimerization or

oligomerization of intracellular proteins. In principle, any two target proteins can be induced to associate by treating the cells or organisms that harbor them with cell permeable, synthetic ligands. To illustrate the practice of this invention, we have induced: (1) the intracellular aggregation of the cytoplasmic tail of the .zeta. chain of the T cell receptor (TCR)-CD3 complex thereby leading to signaling and transcription of a reporter gene, (2) the homodimerization of the cytoplasmic tail of the Fas receptor thereby leading to cell-specific **apoptosis** (programmed **cell death**) and (3)

the heterodimerization of a DNA-binding domain (Gal4) and a transcription-activation domain (VP16) thereby leading to direct transcription of a reporter gene. Regulated intracellular protein association with our cell permeable, synthetic ligands offers new capabilities in biological research and medicine, in particular, in gene

therapy. Using gene transfer techniques to introduce our artificial receptors, one can turn on or off the signaling pathways that lead to the overexpression of therapeutic proteins by administering orally active "dimerizers" or "de-dimerizers", respectively. Since cells from different recipients can be configured to have the pathway overexpress different therapeutic proteins for use in a variety of disorders, the dimerizers have the potential to serve as "universal drugs". They can also be viewed as cell permeable, organic replacements for therapeutic antisense agents or for proteins that would otherwise require intravenous injection or intracellular expression (e.g., the LDL receptor or the CFTR protein).

L35 ANSWER 8 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
 AN 2001-016296 [02] WPIDS  
 CR 2000-475722 [39]; 2000-491087 [42]; 2000-491116 [42]; 2000-491166 [42];  
 2000-572155 [50]  
 DNN N2001-012279 DNC C2001-004573  
 TI Identifying patients with breast **cancer** or precancer, by  
 examining a ductal fluid sample for a marker for breast **cancer**  
 or precancer.  
 DC B04 D16 S03  
 IN HUNG, D T  
 PA (PROD-N) PRO DUCT HEALTH INC  
 CYC 91  
 PI WO 2000070349 A1 20001123 (200102)\* EN 44p  
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
 OA PT SD SE SL SZ TZ UG ZW  
 W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ  
 EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK  
 LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI  
 SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW  
 ADT WO 2000070349 A1 WO 2000-US13713 20000517  
 PRAI US 2000-502404 20000210; US 1999-313463 19990517; US 1999-166100  
 19991117; US 1999-473510 19991228  
 AB WO 200070349 A UPAB: 20010110  
 NOVELTY - New methods for identifying a patient having breast  
**cancer** or precancer comprise examining a ductal fluid sample for a  
 marker for breast **cancer** or precancer.  
 DETAILED DESCRIPTION - (A) A novel method for identifying a patient  
 having breast **cancer** or breast precancer comprises:  
 (1) providing a ductal fluid sample from one duct of a breast of a  
 patient, the fluid not mixed with ductal fluid from any other duct of the

breast;

(2) examining the ductal fluid sample to determine the presence of a marker comprising:

(i) a protein, a polypeptide, a peptide, a nucleic acid, a polynucleotide, an mRNA, a small organic molecule, a lipid, a fat, a glycoprotein, a glycopeptide, a carbohydrate, an oligosaccharide, a chromosomal abnormality, a whole cell with a marker molecule, a particle, a secreted molecule, an intracellular molecule, and a complex of multiple molecules;

(ii) RNA, DNA, protein, polypeptide, or peptide form of a marker selected from a receptor, ligand, protein factor, antigen, **antibody**, enzyme, soluble protein, cytosolic protein, cytoplasmic protein, **tumor** suppressor, cell surface antigen, phospholipid, lipoprotein, hormone responsive protein, differentiation associated antigen, proliferation associated antigen, metastasis associated antigen, integral membrane protein, a protein that participates in an **apoptosis** pathway or in a transcriptional activation pathway, a cell adhesion molecule, extracellular matrix protein, proteolipid, cytokine, basement membrane protein, mucin-type glycoprotein, histone, ribonucleoprotein, sialic acid, bone matrix protein, carbohydrate

antigen,

nuclear protein, nuclear phosphoprotein, proto-oncogene, apolipoprotein, serine protease, **tumor** rejection antigen, surfactant protein, **cell death** protein, zinc endoprotease or a trefoil gene;

(iii) RNA, DNA, protein, polypeptide, or peptide form of a marker selected from chemokine, lectin, **integrin**, selectin, keratin, interleukin, taxin, ferritin, lipocalin, laminin, cyclin, relaxin, nuclein, caspase, melanoma-associated antigen, macrophage inflammatory protein, gap junction protein, calcium binding protein, actin binding protein, phospholipid binding protein, heat shock protein, cell cycle protein, activator of tyrosine and tryptophan hydroxylase, a member of

the

**tumor** necrosis factor, transforming growth factor or Bcl2 family of proteins, a Bcl2-interacting protein, a Bcl2-associated protein, a member of the vasopressin/oxytocin family of proteins or a member of the CCAAT/enhancer binding protein family of proteins;

(iv) an enzyme comprising an RNA, DNA, protein, polypeptide or peptide form of an enzyme selected from a phosphorylase, phosphatase, decarboxylase, isoenzyme, kinase, protease, nuclease, peptidase,

protease,

DNase, RNase, aminopeptidase, topoisomerase, phosphodiesterase,

aromatase,

cyclooxygenase, hydroxylase, dehydrogenase, metalloproteinase,

telomerase,

reductase, synthase, elastase, tyrosinase, transferase or a cyclase;

(v) an RNA, DNA, protein, polypeptide or peptide form of a receptor selected from a steroid hormone receptor, growth factor receptor, kinase receptor, G-protein linked receptor, **tumor** necrosis factor (TNF) family receptor, tyrosine kinase receptor, vasopressin receptor, oxytocin receptor or a serine protease receptor;

(vi) an RNA, DNA, protein, polypeptide or peptide form of a factor selected from a growth factor, proteolytic factor, stromal cell factor, epithelial cell factor, angiogenesis factor, epithelial cell factor, angiogenic factor, or a colony stimulating factor;

(vii) an RNA, DNA, protein, polypeptide or peptide form of an inhibitor selected from an inhibitor of a cyclin, an inhibitor of a

cyclin

complex, a serpin, an inhibitor of proteolytic degradation, a tissue inhibitor of a metalloprotease, or an angiogenesis inhibitor;

(viii) a protein, polypeptide, peptide, nucleic acid, polynucleotide, mRNA, small organic molecule, lipid, fat, glycoprotein, glycopeptide, carbohydrate, oligosaccharide, chromosomal abnormality, whole cell having a marker molecule, particle, secreted molecule, intracellular molecule,

or

a complex of molecules; where the marker is capable of differentiating between any 2 of cytological categories consisting of normal, abnormal, hyperplasia, atypia, ductal carcinoma, ductal carcinoma in situ (DCIS), DCIS-low grade (DCIS-LG), DCIS-high grade (DCIS-HG), invasive carcinoma, atypical mild changes, atypical marked changes, atypical ductal hyperplasia (ADH), insufficient cellular material for diagnosis, or sufficient cellular material for diagnosis.

INDEPENDENT CLAIMS are also included for the following:

(1) a method for identifying a patient having breast **cancer** or breast precancer comprising providing a ductal fluid sample from at last one duct of a breast of the patient and examining the ductal fluid sample to determine the presence of a marker comprising an expression product of a gene encoding a nuclear matrix protein; and

(2) a system for diagnosing breast **cancer** or precancer comprising a tool to retrieve ductal fluid from a breast duct, and instructions for use, to determine the presence of a marker as in (A) or (1).

USE - The methods can be used to identify a patient having breast **cancer** or precancer by examining the ductal fluid sample to determine the presence of a marker comprising RNA, DNA, protein, polypeptide, or peptide form of the marker. Markers found in the ductal fluid may assist to identify malignant cells, aspects of malignant indicia, or may confirm such cytological identification. Markers may also help to stage the malignancy or provide other valuable information which might aid in directing a detailed diagnosis and/or viable treatment options.

Dwg.0/0

L35 ANSWER 9 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
 AN 2000-524487 [47] WPIDS  
 DNC C2000-155811  
 TI Combined administration of an angiogenesis inhibiting agent and an anti-tumor immunotherapeutic agent used for inhibiting tumor cell proliferation.  
 DC B04  
 IN CHERESH, D A; GILLIES, S D; LODE, H N; REISFELD, R A  
 PA (LEXI-N) LEXIGEN PHARM CORP; (SCRI) SCRIPPS RES INST  
 CYC 90  
 PI WO 2000047228 A1 20000817 (200047)\* EN 78p  
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
 OA PT SD SE SL SZ TZ UG ZW  
 W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES  
 FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS  
 LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL  
 TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW  
 AU 2000032280 A 20000829 (200062)  
 ADT WO 2000047228 A1 WO 2000-US3483 20000211; AU 2000032280 A AU 2000-32280  
 20000211  
 FDT AU 2000032280 A Based on WO 200047228

PRAI US 1999-119721 19990212

AB WO 200047228 A UPAB: 20000925

NOVELTY - Treating a tumor cell in a patient with an angiogenesis inhibiting agent and an anti-tumor immunotherapeutic agent which comprises

a cell-effector component and a tumor associated antigen targeting component inhibits tumor cell proliferation.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a composition comprising at least one angiogenesis inhibiting agent and at least one anti-tumor immunotherapeutic agent which comprises a cell-effector component joined to a tumor associated antigen targeting component; and

(2) a kit for treating a tumor cell or tumor metastases comprising a package containing an angiogenesis inhibiting agent and an anti-tumor immunotherapeutic agent which comprises a cell-effector component and a tumor associated antigen targeting component.

ACTIVITY - Cytostatic.

Sequential combination of anti-angiogenic alpha v **integrin** antagonist and anti-tumor compartment-specific immunotherapy with antibody-IL-2 fusion protein was carried out on spontaneous hepatic neuroblastoma metastases. Anti-vascular treatment was carried out for 10 days in mice with established primary tumors. After surgical removal of primary tumors, mice received the tumor compartment-specific immunotherapy

by daily intravenous injection of 5 micro g ch14.18-IL-2 fusion protein (x5). The number of spontaneous liver metastases was determined by macroscopic counts of liver foci. Only mice which had been treated sequentially with both agents presented a 1.5-2 log decrease in hepatic metastases in contrast to all controls, where treatment with each agent used as monotherapy was ineffective. Four of eight mice subjected to the combined therapy showed complete absence of hepatic metastases and the remaining animals showed only 1-5 small metastatic lesions. Similar results were obtained from simultaneous combinations of the **integrin** alpha v antagonist with the ch14.18-IL-2 fusion protein.

MECHANISM OF ACTION - alpha v beta 3 antagonist.

USE - Combined administration of the angiogenesis inhibiting agent and anti-tumor immunotherapeutic agent is used to inhibit the proliferation of tumor cells in primary tumors and metastases (claimed). The treatment can also inhibit the formation of additional tumor metastases and lead to tumor **cell death**. The angiogenesis inhibiting agent inhibits the formation of new blood vessels or the enlargement of existing capillary networks into the tissues near a tumor cell.

ADVANTAGE - The tumor compartment specific response is directed to the tumor microenvironment by the tumor associated antigen targeting component.

Dwg.0/4

L35 ANSWER 10 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 2000-505910 [45] WPIDS

DNC C2000-151862

TI Treating brain tumors by administering peptide and antibody antagonists of

the **integrins** alphav, alphavbeta3 or alphavbeta5.

DC B04 D16

IN LAUG, W E

PA (CHIL-N) CHILDRENS HOSPITAL LOS ANGELES

CYC 86

PI WO 2000044404 A2 20000803 (200045)\* EN 62p

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB  
GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU  
LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR  
TT UA UG UZ VN YU ZA ZW

AU 2000027379 A 20000818 (200057)

ADT WO 2000044404 A2 WO 2000-US1949 20000126; AU 2000027379 A AU 2000-27379  
20000126

FDT AU 2000027379 A Based on WO 200044404

PRAI US 2000-489391 20000121; US 1999-118126 19990201

AB WO 200044404 A UPAB: 20000918

NOVELTY - Methods ((I)-(V)) for inhibiting tumor growth, angiogenesis, extracellular matrix (ECM)-dependent cell adhesion, vitronectin-dependent cell migration and for inducing **apoptosis** in brain tumor cells, comprising administering antagonists (peptides and antibodies) of the **integrins** alpha v, alpha v beta 3 or alpha v beta 5, are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a method (I) of inhibiting tumor growth in the brain of a host, comprising administering an antagonists of an **integrin**;

(2) a method (II) for inhibiting angiogenesis in a tumor tissue located in the brain of a host comprising administering a composition comprising an **integrin** antagonist that inhibits angiogenesis;

(3) a method (III) of inhibiting extracellular matrix (ECM)-dependent cell adhesion in brain tumor cells growing in the brain of a host, comprising administering an antagonist to **integrins** alpha v beta 3 or alpha v beta 5;

(4) a method (IV) of inhibiting vitronectin-dependent cell migration in brain tumor cells growing in the brain of a host, comprising administering an antagonist to **integrin** alpha v beta 3; and

(5) a method (V) of inducing **apoptosis** in tumor cells growing in the brain of a host, comprising administering an antagonist of an **integrin**.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - The polypeptides and antibodies antagonize the activity of the **integrins** alpha v, alpha v beta 3 or alpha v beta 5. They also inhibit vitronectin and tenascin-mediated cell adhesion and migration in tumor cells. They further induce direct brain tumor **cell death**.

Non tissue culture dishes were incubated for 1 hour at 37 deg. C with vitronectin, tenascin, fibronectin and/or collagen I (10 micro g/ml), then washed with phosphate buffered saline (PBS). After the wash 5 multiply

105 tumor cells were plated an incubated for 16 hours at 37 deg. C. The cultures were then washed and an adhesion buffer containing 20 micro g/ml of pentapeptide or control peptide were added and incubated for a further 24 hours. The cultures were then washed twice with adhesion buffer and stained with Crystal violet and the optical density at 600 nm (OD600) was determined. The more adherent cells present, the higher the OD600. The tumor cell detached from vitronectin and tenascin, whose adherence was

mediated by alpha v **integrins**, but nit from collagen or fibronectin, which interacted with non alpha v **integrins**. For example with the control peptide, 100% of the tumor cells remained attached to all of the extracellular matrix proteins, whereas the active peptide reduced adhesion the number of cells adhering to 2% (vitronectin) and 40% (tenascin).

USE - The methods and antagonists are used to treat brain tissue tumors.  
Dwg.0/9

L35 ANSWER 11 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
AN 2000-387417 [33] WPIDS  
DNC C2000-117550  
TI Novel in vitro co-culture system and device for the production of lymphoid tissue from hematopoietic progenitor cells.  
DC B04 D16  
IN POZNANSKY, M C; PYKETT, M J; ROSENZWEIG, M; SCADDEN, D T  
PA (CYTO-N) CYTOMATRIX LLC; (GEHO) GEN HOSPITAL CORP  
CYC 23  
PI WO 2000027999 A2 20000518 (200033)\* EN 55p  
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE  
W: AU CA CN JP US  
AU 2000017204 A 20000529 (200041)  
ADT WO 2000027999 A2 WO 1999-US26795 19991112; AU 2000017204 A AU 2000-17204 19991112  
FDT AU 2000017204 A Based on WO 200027999  
PRAI US 1998-107972 19981112  
AB WO 200027999 A UPAB: 20000712

NOVELTY - In vitro production of lymphoid tissue-specific cells, comprising introducing and co-culturing hematopoietic progenitor cells and

lymphoreticular stromal cells into a porous, solid matrix with interconnected pores that permit the cells to grow throughout the matrix, where the lymphoreticular stromal cell support the growth and differentiation of the hematopoietic progenitor cells, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

in vivo maintenance, expansion and/or differentiation of hematopoietic progenitor cells, comprising implanting into a subject an open cell porous, solid matrix with at least 75 % open space, seeded with hematopoietic progenitor cells and lymphoreticular stromal cells;

(1) inducing T cell anergy comprising:

(a) introducing hematopoietic progenitor cells (comprising pluripotent stem cells, multipotent progenitor cells, or progenitor cells committed to specific hematopoietic lineages), antigen presenting cells and lymphoreticular stromal cells into a porous, solid matrix with interconnected pores that permit the cells to grow throughout the matrix; and

(b) co-culturing the cells with at least 1 antigen to induce the formation of T cells and/or T cell progenitors and inhibit the activation of the formed cells;

(2) inducing T cell reactivity comprising:

(a) introducing hematopoietic progenitor cells, antigen presenting cells and lymphoreticular stromal cells into a porous, solid matrix with interconnected pores that permit the hematopoietic progenitor and lymphoreticular stromal cells to grow throughout the matrix; and

(b) co-culturing the cells with at least 1 antigen to induce the formation of T cells and/or T cell progenitors with specificity for the antigen(s);

(3) a composition comprising:

(1) a porous, solid matrix with at least 75 % open space and pores that permit cells to grow throughout the matrix;

(2) sufficient lymphoreticular stromal cells attached to the matrix to support the growth and differentiation of hematopoietic progenitor cells, and

(3) hematopoietic progenitor cells attached to the matrix;

(4) identifying an agent suspected of affecting hematopoietic cell development, comprising:

(a) introducing hematopoietic progenitor and lymphoreticular stromal cells into a porous, solid matrix with interconnected pores that permit the cells to grow throughout the matrix;

(b) co-culturing the cells in a test co-culture in the presence of

at

least 1 candidate agent; and

(c) determining whether the candidate agent(s) affect hematopoietic cell development by comparing the test co-culture hematopoietic cell development to a control co-culture where hematopoietic progenitor and lymphoreticular stromal cells are co-cultured in the absence of the candidate agent(s); and

(5) isolating an agent suspected of affecting hematopoietic cell development from a cell culture, comprising:

(a) introducing hematopoietic progenitor and lymphoreticular stromal cells into an open cell porous, solid matrix with at least 75 % open

space

and with interconnected pores that permit the cells to grow throughout

the

matrix;

(b) co-culturing the cells;

(c) obtaining a test-supernatant from the co-culture;

(d) comparing the test-supernatant to a control-supernatant; and

(e) obtaining a subtraction of the test-supernatant that contains an agent suspected of affecting hematopoietic cell development that is

absent

from the control-supernatant.

USE - The methods are useful for the co-culture of hematopoietic progenitor cells and lymphoreticular stromal cells to produce lymphoid tissue-specific cells. Cells committed to the T lymphoid lineage may be useful for treating T cell disorders and diseases.

ADVANTAGE - The methods produce high numbers of lymphoid tissue-specific cell progeny.

DESCRIPTION OF DRAWING(S) - The diagram shows the intrasample variability in numbers of T cells generated in a co-culture system.

Dwg.2/3

L35 ANSWER 12 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 2000-365610 [31] WPIDS

DNN N2000-273559 DNC C2000-110472

TI **Antibody** modulation of claudin-mediated cell adhesion for increasing vasopermiability, for delivering drugs to **tumors** and the nervous system and across the skin.

DC B04 B07 D16 S03

IN BLASCHUCK, O W; GOUR, B J; SYMONDS, J M

PA (ADHE-N) ADHEREX TECHNOLOGIES INC

CYC 90

PI WO 2000026360 A1 20000511 (200031)\* EN 117p  
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
 OA PT SD SE SL SZ TZ UG ZW  
 W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES  
 FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS  
 LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL  
 TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000010223 A 20000522 (200040)  
 ADT WO 2000026360 A1 WO 1999-CA1029 19991103; AU 2000010223 A AU 2000-10223  
 19991103

FDT AU 2000010223 A Based on WO 200026360

PRAI US 1999-282029 19990330; US 1998-185908 19981103

AB WO 200026360 A UPAB: 20000630

NOVELTY - Polypeptide agents (I) (especially **antibodies**) comprising claudin cell adhesion recognition (CAR) sequences and capable of modulating claudin-mediated cell adhesion, are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

- (1) a cell adhesion modulating agent (I) that:  
 (a) comprises a claudin CAR (cell adhesion recognition) sequence;  
 and  
 (b) contains 3-16 amino acid residues linked by peptide bonds;  
 (2) a polynucleotide (II) encoding (I);  
 (3) an expression vector (III) comprising (II);  
 (4) a host cell (IV) transformed with (III);  
 (5) a method (V) for detecting the presence of claudin expressing cells, comprising contracting a sample with an **antibody** that binds to a claudin comprising a CAR sequence and detecting the level of **antibody**-claudin complexes in the sample;  
 (6) a kit for use in (V) comprising an **antibody** that binds to a claudin comprising a CAR sequence and a detection agent; and  
 (7) a kit (VI) for enhancing drug delivery, comprising a skin patch and (I) (which inhibits claudin-mediated cell adhesion).

ACTIVITY - Cardiovascular; cytostatic; anti-angiogenic; neuroactive; dermatological; apoptotic.

MECHANISM OF ACTION - **Antibody** modulation (claimed) of claudin-mediated cell adhesion.

The mean electrical resistance across MDCK (Mandane Derby canine kidney) cell monolayers cultured for 24 hours in medium alone (control)

or  
 a medium containing Peptide 118 (Ac-WKIYSYAGDN-NH<sub>2</sub>) at various concentrations was determined. It was found that Peptide 118 reduced the electrical resistance across the monolayer in a dose dependent manner (e.g. Control = 300 ohms/cm<sup>2</sup>, 0.062 mg/ml of peptide = 250 ohms/cm<sup>2</sup> and 0.5 mg/ml of peptide = 10 ohms/cm<sup>2</sup>). This demonstrated the ability of, Peptide 118 to inhibit the formation of tight junctions in epithelial cells.

USE - (I) may be used to modulate claudin-mediated cell adhesion,  
 for  
 decreasing undesirable claudin-mediated cell adhesion, for increasing vasopermeability in a mammal (by inhibiting claudin-mediated cell adhesion), for treating **cancer** by enhancing the delivery of a drug through the skin of a mammal, for enhancing the delivery of a drug  
 to  
 a **tumor** in a mammal, for inhibiting angiogenesis, for enhancing drug delivery to the nervous system, for enhancing wound healing, for

enhancing adhesion of foreign tissue implanted within a mammal and for inducing **apoptosis** in cells that express claudin, for detecting cells that express claudin (claimed).  
Dwg.0/4

L35 ANSWER 13 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
AN 2000-160899 [14] WPIDS  
DNN N2000-120030 DNC C2000-050300  
TI Modulating agents for treating autoimmune diseases, **cancer**, spinal cord injuries, and for increasing vasopermeability, inhibiting synaptic stability and preventing pregnancy.  
DC B04 D16 S03  
IN BLASCHUK, O W; DOHERTY, P; GOUR, B J  
PA (ADHE-N) ADHEREX TECHNOLOGIES INC  
CYC 86  
PI WO 2000002917 A2 20000120 (200014)\* EN 144p  
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
OA PT SD SE SL SZ UG ZW  
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB  
GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU  
LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR  
TT UA UG US UZ VN YU ZA ZW  
AU 9945964 A 20000201 (200028)  
ADT WO 2000002917 A2 WO 1999-CA627 19990712; AU 9945964 A AU 1999-45964 19990712  
FDT AU 9945964 A Based on WO 200002917  
PRAI US 1998-113977 19980710  
AB WO 200002917 A UPAB: 20000320  
NOVELTY - A cell adhesion modulating agent (I) capable of binding to the cadherin CAR sequence HAV, where the agent doesn't comprise an **antibody** or antigen-binding fragment of it.  
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:  
(1) a cell adhesion modulating agent (II), comprising an HAV-BM sequence or peptidomimetic of it, a polynucleotide encoding an HVA-BM sequence or an **antibody** or antigen-binding fragment of them which specifically binds to an HAV-BM sequence, the agent modulates a cadherin-mediated process;  
(2) pharmaceutical composition comprising (I) or (II);  
(3) a method for modulating a cadherin-mediated function, comprising contacting a cadherin-expressing cell with (I) or (II);  
(4) a kit for enhancing transdermal drug delivery comprising a skin patch and (I) or (II);  
(5) a method for detecting the presence of cadherin-expressing cells in a sample, comprising contacting the sample with an **antibody** or antigen-binding fragment which binds to an HAV-BM sequence under conditions which allow complex formation, and detecting the level of **antibody**-cadherin complex and detecting the presence of cadherin expressing cells in a sample;  
(6) a method of identifying (I) by contacting the test compound with an **antibody** or antigen-binding fragment specific for an HAV-BM sequence, and detecting the level of the complex binding to test compound;  
(7) a method for facilitating **blood** sampling in a mammal, comprising contacting epithelial cells of a mammal with (I) or (II), which inhibits cadherin mediated cell adhesion and the step of contacting is

performed to allow passage of one or more **blood** components across the epithelial cells; and

(8) a kit for sampling **blood** by the skin or gum of a mammal comprising a skin patch, (I) comprising a cyclic peptide and reagent.

ACTIVITY - Antiapoptotic; cytostatic. The disruption of **tumor** cell adhesion by using 1 mg/ml of N-Ac-INPISGQ was tested using monolayer cultures of human ovarian **cancer** SKOV3 cells and SKOV3 cells retracted from one another in the presence of this peptide.

MECHANISM OF ACTION - Modulator of cell adhesion molecule.

USE - (I) is used for inhibiting or enhancing cadherin mediated functions like cell adhesion, neurite outgrowth, Schwann cell migration and synaptic stability in cells preferably epithelial, endothelial, neural, **tumor** cells and **lymphocytes** expressing cadherin E or N (claimed). Inhibition of cadherin mediated cell adhesion by (I) is used in reducing unwanted cellular adhesion, enhancing drug delivery through skin, drug delivery to a **tumor**, treating **cancer** and/or inhibiting metastasis, inducing **apoptosis**, inhibiting angiogenesis, modulating immune system, preventing pregnancy, increasing vasopermeability, inhibiting synaptic stability in a mammal. Enhancement is used for facilitating wound healing, enhancing adhesion of foreign tissue implant, enhancing and/or directing neurite outgrowth and treating spinal cord injuries. (I) is used for treating demyelinating neurological diseases and for facilitating **blood** sampling in a mammal. (I) is used for detecting cadherin expressing cells in a sample

by

detecting the level of **antibody** cadherin complex. (All claimed).

ADVANTAGE - These agents does not produce undesirable side effects and invasive procedures for administration is not required.  
Dwg.0/8

L35 ANSWER 14 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
AN 2000-160898 [14] WPIDS  
DNC C2000-050299  
TI Polypeptide useful in modulating cell-cell interaction in tissues of heart, brain, spinal cord and treating chondro sarcoma, atherosclerosis, restenosis, obesity, intimal hyperplasia and **tumors**.  
DC B04 D16  
IN BAINBUR, N; BISHOP, P D; DEISHER, T A; SHEPPARD, P O  
PA (ZYMO) ZYMOGENETICS INC  
CYC 85  
PI WO 2000002912 A2 20000120 (200014)\* EN 133p  
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
OA PT SD SE SL SZ UG ZW  
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB  
GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU  
LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR  
TT UA UG UZ VN YU ZA ZW  
AU 9949833 A 20000201 (200028)  
ADT WO 2000002912 A2 WO 1999-US15638 19990709; AU 9949833 A AU 1999-49833 19990709  
FDT AU 9949833 A Based on WO 200002912  
PRAI US 1998-113883 19980710  
AB WO 200002912 A UPAB: 20000320  
NOVELTY - An isolated z dint polypeptide (I), homologous to disintegrin-like family members, comprising a contiguous sequence of 14 amino acids of a 696 residue amino acid sequence (II), fully defined in the specification, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated polypeptide (III) selected from the polypeptide comprising residues 164-382, 383-464, 465-696, 438-449, 164-464, 164-696, 383-696, 164-449, 438-696 and 1-696 of (II);

(2) an isolated polynucleotide molecule encoding a polypeptide molecule a contiguous sequence of 14 amino acids of (II);

(3) an isolated polynucleotide encoding a fusion protein having two segments one, positioned amino terminally to the other, encoding a protease domain and the other encoding polypeptide comprising contiguous sequence of 14 amino acids of (II);

(4) an isolated polynucleotide molecule encoding a polypeptide is a polynucleotide molecule encoding a polypeptide at least 80% identical to residues 383-464 of (II) or its complement;

(5) an expression vector (IV) comprising a transcription promoter, DNA encoding (I) and a terminator, all operably linked;

(6) a cell (V) into which (IV) has been introduced;

(7) producing (I), comprising culturing (V) and recovering (I);

(8) an isolated polypeptide (VI) comprising contiguous sequence of amino acids selected from KRRKRA, LKRRKR, GKDGDR, KDEGPK and KKHRSS;

(9) an isolated polynucleotide encoding (I), (III) or (VI); and

(10) a method for modulating cell-cell interaction by combining (I) with cells in vivo and in vitro.

ACTIVITY - Antiarteriosclerotic; anorectic; vasotropic; anticoagulant; nootropic; neuroprotective. Zdint was analyzed for its ability to inhibit platelet accumulation at sites of arterial thrombosis due to mechanical injury in non-human primates. Aortic endarterectomy was done in baboons, as described in Lumsden et al (**Blood** 81:

1762-1770 (1993)). Prior to opening of the shunt to the circulating **blood**, In111-labeled autologous platelets were injected

intravenously into the animal. The level of platelet accumulation at the site of the injured artery was determined. Zdint1 was given using bolus injections prior to the opening of the shunt. The injured arteries were measured continuously for 60 minutes. The results show that zdint

inhibits

platelet accumulation.

MECHANISM OF ACTION - (I) is a cardiac myocyte proliferation and differentiation stimulator, adipocyte proliferation and differentiation inhibitor. Polynucleotides encoding (I) are used in gene therapy.

USE - (I) is useful in modulating cell-cell interactions of the cells

derived from tissues of heart, brain, spinal cord and skeletal muscle (claimed). (I) is useful in treating and diagnosing chondrosarcoma, atherosclerosis, Alzheimer's disease, restenosis, ischemic reperfusion, obesity, intimal hyperplasia and **tumors** of heart, brain, and spinal cord. (I) is also useful in identifying its new family members, antagonists, agonists and **antibodies**. Antagonists, **antibodies** and fusion proteins of (I) are useful in inhibiting platelet aggregation, **apoptosis**, neurogenesis and myogenesis. Agonists and antagonists are useful in studying cell-cell interactions, arthritis, myogenesis, neurogenesis, connective tissue disorders, chondrogenesis, **tumor** proliferation and suppression, extracellular matrix proteins, repair and remodeling of ischemia reperfusion, inflammation, and **apoptosis**. Polynucleotides encoding (II) are useful as probes and primers to clone 5' non-coding region of zdint gene, and in gene therapy to increase or inhibit, using antisense, zdint activity. (I) and polynucleotides encoding it are useful

to identify and isolate receptors and **integrins** involved in cell-cell interactions.

ADVANTAGE - (I) or its **antibody** even when conjugated with beta -emitting radionuclide is less dangerous than conventional radioactive therapies.

Dwg.0/2

L35 ANSWER 15 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
AN 2000-531471 [48] WPIDS  
CR 1993-303150 [38]; 1996-097460 [10]; 1997-434333 [40]; 1998-397937 [34];  
1999-105025 [09]; 1999-131255 [11]; 1999-189722 [16]; 1999-579890 [49];  
2000-072047 [06]; 2000-269871 [22]; 2000-363766 [28]  
DNC C2000-158393  
TI New immunological and growth factor-based bispecific binding ligands,  
useful for stimulating coagulation in vasculature-associated diseases,  
e.g. for treating both benign and malignant diseases (e.g. meningioma or  
hemangioma).  
DC B04 D16  
IN EDGINGTON, T S; THORPE, P E  
PA (SCRI) SCRIPPS RES INST; (TEXA) UNIV TEXAS SYSTEM  
CYC 1  
PI US 6093399 A 20000725 (200048)\* 83p  
ADT US 6093399 A CIP of US 1992-846349 19920305, CIP of US 1994-205330  
19940302, CIP of US 1994-273567 19940711, US 1995-482369 19950607  
PRAI US 1995-482369 19950607; US 1992-846349 19920305; US 1994-205330  
19940302; US 1994-273567 19940711  
AB US 6093399 A UPAB: 20001001  
NOVELTY - A binding ligand (I) comprising a first binding region that is  
operatively linked to a coagulation factor, or a second binding region  
that binds to a coagulation factor, is new.  
DETAILED DESCRIPTION - A binding ligand (I) comprising a first  
binding region that binds to a component expressed, accessible to binding  
or localized on the surface of a tumor cell, intratumoral vasculature or  
tumor stroma, is new. The first binding region is operatively linked to a  
coagulation factor, or a second binding region that binds to a  
coagulation factor. The second binding region comprises an antibody or an antigen  
binding region of an antibody.  
INDEPENDENT CLAIMS are also included for the following:  
(1) a binding ligand comprising a first binding region that binds to  
a component expressed, accessible to binding or localized on the surface  
of intratumoral vasculature or stroma, where the first binding region is  
operatively linked to a coagulant or an antibody, or an antigen binding  
region that binds to a coagulant;  
(2) a binding ligand comprising a first antibody or its antigen  
binding region, which binds to a component expressed, accessible to  
binding or localized on the surface of intratumoral vasculature or  
stroma,  
where the first antibody or antigen binding region is operatively linked  
to a coagulant or to a second antibody, or antigen binding region that  
binds to a coagulant;  
(3) binding ligands comprising a first antibody or its antigen  
binding region, which binds to a marker expressed, accessible to binding  
or localized on the cell surface of intratumoral blood vessels of a  
vascularized tumor, where the first antibody or antigen binding region is  
linked to a coagulant or to a second antibody, or its antigen binding  
region that binds to a coagulant;

(4) a conjugate comprising a first antibody or its antigen binding portion that binds to a marker expressed or localized on the cell surface of intratumoral blood vessels of a vascularized tumor, where the first antibody or antigen binding portion is linked to a coagulant or a second antibody, or an antigen binding region that binds to a coagulant;

a (5) binding ligands comprising a first binding region that binds to component expressed, accessible to binding or localized on the surface of a tumor cell, established intratumoral vasculature, tumor-associated vasculature or tumor stroma, where the first binding region is operatively linked to a coagulation factor or to an antibody or its antigen binding region that binds to a coagulation factor; and

(6) a pharmaceutical composition comprising (I).

ACTIVITY - Cytostatic; coagulant. A20 cells coated with B21-2/10H10 complex and truncated Tissue Factor (tTF) were capable of inducing fibrin formation, it shortened coagulation time from 140 seconds (the time for mouse plasma in CaCl<sub>2</sub> to coagulate in the absence of added antibodies or TF under specific conditions) to 60 seconds. Mouse plasma added to A20 cells to which tTF had been tethered with B21-2/10H10 coagulated rapidly. Fibrin strands were visible 36 seconds after addition of plasma as compared with 164 seconds in plasma added to untreated A20 cells.

MECHANISM OF ACTION - Thrombin stimulator. For establishment of solid tumors, 1.5 multiply 10<sup>7</sup> C1300 cells were injected subcutaneously into the right anterior flank of BALB/c nu/nu mice. When tumors had grown to 0.8 cm in diameter, mice were randomly assigned to treatment groups each containing 7-8 mice. Mice 0.8 cm diameter tumors administered with the coaguligand, composed of B21-2/10H10 and tTF, showed tumor regression to approximately half their pre-treatment size. Repeated treatment on the 7th day caused the tumors to regress further, usually completely. In 5/7 animals, complete regressions were obtained. These anti-tumor effects were statistically highly significant (P is less than 0.001) when compared with all other groups.

USE - The binding ligand is useful for effectively promoting coagulation in intratumoral blood vessels when administered to a subject having vascularized tumor (claimed). It is useful in achieving specific coagulation, e.g. coagulation in tumor vasculature. Furthermore, the binding ligand is useful for stimulating coagulation in vasculature-associated diseases. Particularly, the binding ligand is useful for treating both benign and malignant diseases that have a vascular component. These diseases include benign growths (e.g. BPH), diabetic retinopathy, arteriovenous malformations, meningioma, hemangioma, neovascular glaucoma, psoriasis, synovitis, endometriosis, hemophylic joints, hypertrophic scars or vascular adhesions. The binding ligands may also be combined with anti-tumor therapy (e.g. radiotherapy or chemotherapy).

ADVANTAGE - Immunotoxins have proven effective at treating lymphomas and leukemias. However, immunotoxins are ineffective in the treatment of solid tumors. Another problem is that antigen-deficient mutants can escape

being killed by the immunotoxin and regrow. The present binding ligands offer several advantages. Firstly, the target cells are directly accessible to intravenously administered ligands, permitting rapid localization of high percentage of the injected dose. Secondly, since each capillary provides oxygen and nutrients for thousands of cells in its surrounding cord of tumor, even limited damage to the tumor vasculature could produce an avalanche of tumor **cell death**. Finally, the outgrowth of mutant endothelial cells, lacking a target antigen, is unlikely because they are normal cells. Thus, the binding ligands are safer for use in humans than that of targeting a toxin to tumor vasculature.

Dwg.0/8

L35 ANSWER 16 OF 37 HCAPLUS COPYRIGHT 2001 ACS

AN 2000:53434 HCAPLUS

DN 132:106961

TI Cancer treatment methods using therapeutic conjugates that bind to aminophospholipids

IN Thorpe, Philip E.; Ran, Sophia

PA Board of Regents, the University of Texas System, USA

SO PCT Int. Appl., 266 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000002587	A1	20000120	WO 1999-US15668	19990712
	W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	AU 9950958	A1	20000201	AU 1999-50958	19990712
PRAI	US 1998-92589		19980713		
	US 1998-110600		19981202		
	WO 1999-US15668		19990712		
AB	Disclosed is the surprising discovery that aminophospholipids, such as phosphatidylserine and phosphatidylethanolamine, are specific, accessible and stable markers of the luminal surface of tumor blood vessels. The present invention thus provides aminophospholipid-targeted diagnostic and therapeutic constructs for use in tumor intervention.				
Antibody-therapeutic	agent conjugates and constructs that bind to aminophospholipids are particularly provided, as are methods of specifically delivering therapeutic agents, including toxins and coagulants, to the stably-expressed aminophospholipids of tumor blood vessels, thereby inducing thrombosis, necrosis and tumor regression.				

RE.CNT 10

RE

(1) Diaz, C; BIOCONJUGATE CHEMISTRY 1998, V9(2), P250 HCAPLUS

(3) Kuriyama, S; WO 9829453 A 1998 HCAPLUS

(4) Neorx Corp; WO 9843678 A 1998 HCAPLUS  
 (5) Ran, S; CANCER RESEARCH 1998, V58(20), P4646 HCAPLUS  
 (6) Rauch, J; LUPUS 1996, V5, P498 HCAPLUS  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 17 OF 37 HCAPLUS COPYRIGHT 2001 ACS  
 AN 2000:53432 HCAPLUS  
 DN 132:106960  
 TI Cancer treatment methods using antibodies to aminophospholipids  
 IN Thorpe, Philip E.; Ran, Sophia  
 PA Board of Regents, the University of Texas System, USA  
 SO PCT Int. Appl., 226 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000002584	A2	20000120	WO 1999-US15600	19990712
	WO 2000002584	A3	20000330		
	W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	AU 9954585	A1	20000201	AU 1999-54585	19990712
PRAI	US 1998-92672		19980713		
	US 1998-110608		19981202		
	WO 1999-US15600		19990712		
AB	Disclosed are the surprising discoveries that aminophospholipids, such as phosphatidylserine and phosphatidylethanolamine, are stable and specific markers accessible on the luminal surface of tumor blood vessels, and that the administration of an anti-aminophospholipid antibody alone is sufficient to induce thrombosis, tumor necrosis and tumor regression in vivo . This invention therefore provides anti-aminophospholipid antibody-based methods and compns. for use in the specific destruction of tumor blood vessels and in the treatment of solid tumors. Although various antibody conjugates and combinations are thus provided, the use of naked, or unconjugated, anti-phosphatidylserine antibodies is a particularly important aspect of the invention, due to simplicity and effectiveness of the approach.				

L35 ANSWER 18 OF 37 HCAPLUS COPYRIGHT 2001 ACS  
 AN 2000:275313 HCAPLUS  
 DN 132:313670  
 TI Coated substrates for blood, plasma, or tissue washing and columns equipped with these substrates  
 IN Dunzendorfer, Udo; Will, Gottfried  
 PA Germany  
 SO Ger. Offen., 30 pp.  
 CODEN: GWXXBX

DT Patent

LA German

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19845286	A1	20000427	DE 1998-19845286	19981001
	EP 1004598	A2	20000531	EP 1999-118541	19990918
	EP 1004598	A3	20000607		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRAI DE 1998-19845286 19981001

AB Columns, filters, cannulas, etc. contg. substrates coated with specific antibodies can be used during plasmapheresis to remove pathogenic cytokines such as tumor necrosis factor (TNF), anti-TNF, fragments of TNF or anti-TNF, or TNF transport proteins from blood, plasma, or tissues. The substrates may addnl. be coated with antibodies to microbial or viral pathogens or mixts. of pathogens as well as to polysaccharide antigens, viral capsids, microbial antigens, reverse transcriptase, endothelin, protein A, etc. Selective removal of these pathogens, antigens, proteins,

etc. leaves all normal plasma components unchanged and obviates the need for supplementation of the plasma with these components. Suitable substrates include polymers, polymer-coated metals, cellulose derivs., starch, and Sepharose; these may be derivatized for covalent binding of the pathogens or pathogenic mols. Thus, Escherichia coli pyelonephritis was successfully treated by plasmapheresis coupled with columns loaded with anti-TNF-.alpha. for 14 days, 4 h/day, as detd. by decreases in plasma TNF-.alpha. levels and colony counts in urine cultures.

L35 ANSWER 19 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
DUPLICATE

2

AN 1999-229225 [19] WPIDS

DNC C1999-067426

TI **Monoclonal** antibody against human **integrin**-associated protein, useful as remedies e.g. in treatment of lymphatic leukemia and myelocytic leukemia.

DC B04 D16

IN FUKUSHIMA, N; UNO, S

PA (CHUS) CHUGAI SEIYAKU KK; (CHUS) CHUGAI PHARM CO LTD

CYC 82

PI WO 9912973 A1 19990318 (199919)\* JA 51p  
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
OA PT SD SE SZ UG ZW  
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE  
GH GM HR HU ID IL IS KE KG KR KZ LC LK LR LS LT LU LV MD MG MK MN  
MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ  
VN YU ZW

AU 9890028 A 19990329 (199932)

JP 11155569 A 19990615 (199934) 18p

NO 2000001238 A 20000511 (200034)

EP 1035132 A1 20000913 (200046) EN

R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

CZ 2000000907 A3 20000816 (200048)

SK 2000000323 A3 20000912 (200055)

ADT WO 9912973 A1 WO 1998-JP4118 19980911; AU 9890028 A AU 1998-90028  
19980911; JP 11155569 A JP 1998-276603 19980911; NO 2000001238 A WO

1998-JP4118 19980911, NO 2000-1238 20000309; EP 1035132 A1 EP 1998-941848  
19980911, WO 1998-JP4118 19980911; CZ 2000000907 A3 WO 1998-JP4118  
19980911, CZ 2000-907 19980911; SK 2000000323 A3 SK 2000-323 19980911  
FDT AU 9890028 A Based on WO 9912973; EP 1035132 A1 Based on WO 9912973; CZ  
2000000907 A3 Based on WO 9912973  
PRAI JP 1997-264853 19970911  
AB WO 9912973 A UPAB: 19990518  
NOVELTY - A **monoclonal** antibody can induce **apoptosis**  
of nucleated blood cells with **integrin**-associated protein.  
DETAILED DESCRIPTION - DETAILED DESCRIPTION - A **monoclonal**  
antibody can induce **apoptosis** of nucleated blood cells with  
**integrin**-associated protein (IAP).  
INDEPENDENT CLAIMS are also included for:  
(1) a **monoclonal** antibody fragment, peptide or low  
molecular weight compound which can induce **apoptosis** of  
nucleated blood cells with **IAP**; and  
(2) a hybridoma that can produce the antibody.  
ACTIVITY - Inducing **apoptosis** of nucleated blood cells;  
antigenic effect  
MECHANISM OF ACTION - **Apoptosis** inducers; antibodies.  
USE - The **monoclonal** antibody against human  
**integrin**-associated protein, including a **monoclonal**  
antibody fragment, peptide and low molecular weight compound, can be used  
as remedies, particularly for treatment of lymphatic leukemia (claimed)  
and myelocytic leukemia.  
DESCRIPTION OF DRAWING(S) - Expression amount of human **IAP**  
in the presence of anti-CD47 antibody of human **IAP**-expressing  
L1210 cells: peak = the control of pCOS1 gene-introduced L1210 cells.  
Dwg.2/21

L35 ANSWER 20 OF 37 USPATFULL  
AN 1999:136968 USPATFULL  
TI Product and process to regulate actin polymerization in T  
**lymphocytes**  
IN Finkel, Terri H., Englewood, CO, United States  
Rozdzial, Moshe M., Louisville, CO, United States  
PA National Jewish Medical and Research Center, Denver, CO, United States  
(U.S. corporation)  
PI US 5976819 19991102  
AI US 1995-563892 19951121 (8)  
DT Utility  
EXNAM Primary Examiner: Saunders, David  
LREP Sheridan Ross P.C.  
CLMN Number of Claims: 22  
ECL Exemplary Claim: 1  
DRWN 5 Drawing Figure(s); 5 Drawing Page(s)  
LN.CNT 2007  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
AB The present invention relates to methods to regulate actin  
polymerization in T **lymphocytes** involved in tumorigenesis,  
inflammatory responses, immune responses, allergic responses and graft  
rejection responses, kits to perform such assays and methods to  
identify  
regulatory reagents that specifically control actin polymerization in T  
**lymphocytes**.

L35 ANSWER 21 OF 37 USPATFULL

AN 1999:75768 USPATFULL  
 TI Mammalian **IAP antibodies** and diagnostic kits  
 IN Korneluk, Robert G., Ottawa, Canada  
 MacKenzie, Alexander E., Ottawa, Canada  
 Baird, Stephen, Ottawa, Canada  
 PA University of Ottawa, Ottawa, Canada (non-U.S. corporation)  
 PI US 5919912 19990706  
 AI US 1995-511485 19950804 (8)  
 DT Utility  
 EXNAM Primary Examiner: Eisenschenk, Frank C.; Assistant Examiner: Nolan, Patrick J.  
 LREP Clark & Elbing LLP; Bieker-Brady, Kristina  
 CLMN Number of Claims: 26  
 ECL Exemplary Claim: 1  
 DRWN 11 Drawing Figure(s); 25 Drawing Page(s)  
 LN.CNT 2172  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB Disclosed is substantially pure DNA encoding mammalian **IAP** polypeptides; substantially pure polypeptides; and methods of using such  
 DNA to express the **IAP** polypeptides in cells and animals to inhibit **apoptosis**. Also disclosed are conserved regions characteristic of the **IAP** family and primers and probes for the identification and isolation of additional **IAP** genes. In addition, methods for treating diseases and disorders involving **apoptosis** are provided.

L35 ANSWER 22 OF 37 USPATFULL  
 AN 1999:75500 USPATFULL  
 TI Methods and compositions for the use of apurinic/apyrimidinic endonucleases  
 IN Kelley, Mark R., Zionsville, IN, United States  
 Duguid, John, Brownsburg, IN, United States  
 Eble, John, Indianapolis, IN, United States  
 PA Advanced Research & Technology Institute, Bloomington, IN, United States  
 (U.S. corporation)  
 PI US 5919643 19990706  
 AI US 1997-872719 19970611 (8)  
 PRAI US 1996-19561 19960611 (60)  
 US 1996-19602 19960611 (60)  
 DT Utility  
 EXNAM Primary Examiner: Patterson, Jr., Charles L.  
 LREP Arnold, White & Durkee  
 CLMN Number of Claims: 15  
 ECL Exemplary Claim: 1  
 DRWN 57 Drawing Figure(s); 21 Drawing Page(s)  
 LN.CNT 4677  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB Disclosed are methods and compositions for identifying, monitoring and treating premalignant and malignant conditions in a human subject. The present invention further discloses methods and compositions for determining cells undergoing **apoptosis**, and for increasing the efficacy of a cancer therapy. The methods involve the use of apurinic/apyrimidinic endonuclease (APE), independently, as a marker for  
 (pre)malignant conditions and for **apoptosis**. Also described

are polyclonal **antibody** preparations for use in methods for detecting APE and methods for modulating expression susceptibility of cells to **apoptosis**.

L35 ANSWER 23 OF 37 USPATFULL

AN 1999:19001 USPATFULL

TI Regulated transcription of targeted genes and other biological events

IN Crabtree, Gerald R., Woodside, CA, United States

Schreiber, Stuart L., Cambridge, MA, United States

Spencer, David M., Los Altos, CA, United States

Wandless, Thomas J., Cambridge, MA, United States

Belshaw, Peter, Cambridge, MA, United States

PA President and Fellows of Harvard College, Cambridge, MA, United States (U.S. corporation)

Board of Trustees of Leland S. Stanford Jr. University, Stanford, CA, United States (U.S. corporation)

PI US 5869337 19990209

AI US 1995-388653 19950214 (8)

RLI Continuation-in-part of Ser. No. US 1994-196043, filed on 11 Feb 1994 And Ser. No. US 1994-292597, filed on 18 Aug 1994, now patented, Pat. No. US 5834266, each Ser. No. US which is a continuation-in-part of Ser. No. US 1994-179748, filed on 7 Jan 1994, now abandoned which is a continuation-in-part of Ser. No. US 1993-92977, filed on 16 Jul 1993, now abandoned which is a continuation-in-part of Ser. No. US

1993-17931, filed on 12 Feb 1993, now abandoned, said Ser. No. US 292597 which is

a

continuation-in-part of Ser. No. US 1994-179148, filed on 7 Jan 1994, now abandoned which is a continuation-in-part of Ser. No. US

1993-93499,

filed on 16 Jul 1993, now abandoned which is a continuation-in-part of Ser. No. US 17931

DT Utility

EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Schwartzman, Robert

LREP Vincent, Matthew P.; Clauss, Isabelle M.Foley, Hoag & Eliot LLP

CLMN Number of Claims: 165

ECL Exemplary Claim: 85

DRWN 37 Drawing Figure(s); 36 Drawing Page(s)

LN.CNT 4716

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Dimerization and oligomerization of proteins are general biological control mechanisms that contribute to the activation of cell membrane receptors, transcription factors, vesicle fusion proteins, and other classes of intra- and extracellular proteins. We have developed a general procedure for the regulated (inducible) dimerization or oligomerization of intracellular proteins. In principle, any two target proteins can be induced to associate by treating the cells or organisms that harbor them with cell permeable, synthetic ligands. To illustrate the practice of this invention, we have induced: (1) the intracellular aggregation of the cytoplasmic tail of the .zeta. chain of the T cell receptor (TCR)-CD3 complex thereby leading to signaling and transcription of a reporter gene, (2) the homodimerization of the cytoplasmic tail of the Fas receptor thereby leading to cell-specific **apoptosis** (programmed **cell death**) and (3) the heterodimerization of a DNA-binding domain (Gal4) and a transcription-activation domain (VP16) thereby leading to direct

transcription of a reporter gene. Regulated intracellular protein association with our cell permeable, synthetic ligands offers new capabilities in biological research and medicine, in particular, in gene therapy.

L35 ANSWER 24 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
 AN 2000-116364 [10] WPIDS  
 DNC C2000-035508  
 TI New molecules of the apoptotic inhibitor protein 6 (AIP-6) family useful for treating conditions with aberrant AIP-6 expression.  
 DC B04 D16  
 IN YOWE, D  
 PA (MILL-N) MILLENIUM PHARM INC  
 CYC 85  
 PI WO 9962943 A2 19991209 (200010)\* EN 107p

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
 OA PT SD SE SL SZ UG ZW  
 W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB  
 GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV  
 MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT  
 UA UG US UZ VN YU ZA ZW

AU 9945452 A 19991220 (200021)  
 ADT WO 9962943 A2 WO 1999-US12265 19990602; AU 9945452 A AU 1999-45452  
 19990602

FDT AU 9945452 A Based on WO 9962943

PRAI US 1998-87761 19980602

AB WO 9962943 A UPAB: 20000228

NOVELTY - A gene encoding an apoptotic inhibitor protein 6 (AIP-6), an intracellular protein that is predicted to be a member of the IAP (inhibitor of **apoptosis**) superfamily, is new.

DETAILED DESCRIPTION - An isolated nucleic acid is selected from the following group:

(a) a nucleic acid molecule comprising a sequence which is at least 55% identical to the 1219 base pair nucleotide sequence (I), given in the specification, or nucleotides 104-1219 (II) of (I), the cDNA insert of the plasmid deposited with ATCC as Accession Number 209860 (P1), or a complement of this;

(b) a nucleic acid molecule comprising a fragment of at least 300 nucleotides of the nucleotide sequence of (I) or (II), or complement;

(c) a nucleic acid molecule which encodes a polypeptide comprising a 372 amino acid sequence (III), given in the specification, or amino acids 324-358 (IV) of (III) or an amino acid sequence encoded by the cDNA

insert of the plasmid (P1);

(d) a nucleic acid molecule which encodes a fragment of a polypeptide comprising the amino acid sequence (III) comprising at least 15

contiguous amino acids of sequence (III) or (IV) the polypeptide encoded by the cDNA insert of plasmid (P1); and

(e) a nucleic acid molecule which encodes a naturally occurring variant of a polypeptide comprising the amino acid sequence of (III) or (IV) or an amino acid sequence encoded by the cDNA of the plasmid (P1), where the nucleic acid molecule hybridizes to a nucleic acid molecule comprising sequence (I) or (II) under stringent conditions.

INDEPENDENT CLAIMS are also included for the following:

- (1) a host cell which contains the nucleic acid molecule;
  - (2) an isolated polypeptide selected from the following group:
    - (a) a fragment of a polypeptide comprising the amino acid sequence (III) or (IV) where the fragment comprises at least 15 contiguous amino acids of (III) or (IV);
    - (b) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of (III) or (IV) or an amino acid sequence encoded by the cDNA insert of the plasmid (P1), where the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising sequence (I) or (II) under stringent conditions;
    - (c) a polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 55% identical to a nucleic acid comprising the nucleotide sequence of sequence (I) or (II);
  - (3) an **antibody** which selectively binds to the polypeptide of (2);
  - (4) a method (M1) for producing a polypeptide selected from the following group:
    - (a) a polypeptide comprising the amino acid sequence (III) or (IV)
- or
- an amino acid sequence encoded by the cDNA insert of plasmid (P1);
  - (b) a fragment of a polypeptide as in (a) where the fragment comprises at least 15 contiguous amino acids of sequence (III) or (IV) or an amino acid sequence encoded by the cDNA insert of plasmid (P1);
  - (c) a naturally occurring allelic variant of a polypeptide as in (2b). The method involves culturing the host cell of claim (1) under conditions in which the nucleic acid molecule is expressed.
  - (5) a method (M2) for detecting the presence of a polypeptide of (2) in a sample by contacting the sample with a compound which selectively binds to the polypeptide and determining whether the compound binds to the polypeptide in the sample;
  - (6) a method (M3) for detecting the presence of the nucleic acid molecule in a sample by contacting the sample with a nucleic acid probe
- or
- primer which selectively hybridizes to the nucleic acid molecule and determining whether binding occurs;
  - (7) a method (M4) for identifying a compound which binds to a polypeptide of (2) by contacting a polypeptide or a cell expressing the polypeptide with a test compound and determining whether the polypeptide binds;
  - (8) a method (M5) for modulating the activity of a polypeptide of (2) by contacting a polypeptide or a cell expressing the polypeptide of (2) with a compound that binds to the polypeptide in a sufficient concentration to modulate the activity of the polypeptide;
  - (9) a method (M6) for identifying a compound which modulates the activity of a polypeptide of (2) by contacting the polypeptide with a test compound and determining the effect of the test compound on the activity of the polypeptide;
  - (10) a kit comprising a compound which selectively binds to the polypeptide of (2), or a compound which selectively hybridizes to the nucleic acid molecule (N1).

ACTIVITY - Anticancer, immunosuppressive, antiviral.

MECHANISM OF ACTION - Regulation of cellular proliferation and

differentiation and cell survival. The apoptotic inhibitor protein (AIP)-6

molecules are predicted to modulate the apoptotic **cell death** pathway.

USE - The methods of the invention are used to treat a subject having

a disorder characterized by aberrant AIP-6 protein or nucleic acid expression or activity by administering an agent which is an AIP-6 modulator. These disorders include the following: **cancer** (particularly follicular lymphomas, carcinomas associated with mutations in p53 and hormone-dependent **tumors** such as breast **cancer**, prostate **cancer** and ovarian **cancer**), autoimmune disorder (such as systemic lupus erythematosus,

immune-mediated

glomerulonephritis) and viral infections (such as those caused by herpes viruses, pox virus and adenoviruses); neurological diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and various forms of cerebellar degeneration; hematological diseases including anemia; disorders of **blood** cell production; myocardial infarctions and stroke. The nucleic acid molecules, proteins, protein homologues and **antibodies** can be used in screening assays, detection assays (chromosomal mapping, tissue typing, forensic medicine), predictive medicine (diagnostic assays, prognostic assays) and methods of treatment. The AIP-6 proteins can be used for drug screening. The AIP-6 nucleic acid molecules, AIP-6 proteins and anti-AIP- **antibodies** can be incorporated into pharmaceutical compositions suitable for

administration.

Dwg.0/3

L35 ANSWER 25 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 1999-527367 [44] WPIDS

DNN N1999-390641 DNC C1999-154885

TI New peptides, peptide-derived mimetics useful in novel cancer therapy targeted specifically at tumor cells.

DC B04 D16 S03

IN ILANTZIS, C; ORDONEZ-GARCIA, C; SCREATON, R A; STANNERS, C P; TAHERI, M

PA (UYMC-N) UNIV MCGILL

CYC 85

PI WO 9941370 A1 19990819 (199944)\* EN 48p

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
OA PT SD SE SZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD  
GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV  
MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT  
UA UG US UZ VN YU ZW

AU 9925064 A 19990830 (200003)

EP 1053314 A1 20001122 (200061) EN

R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

ADT WO 9941370 A1 WO 1999-CA119 19990211; AU 9925064 A AU 1999-25064 19990211;

EP 1053314 A1 EP 1999-904651 19990211, WO 1999-CA119 19990211

FDT AU 9925064 A Based on WO 9941370; EP 1053314 A1 Based on WO 9941370

PRAI CA 1998-2224129 19980212

AB WO 9941370 A UPAB: 19991026

NOVELTY - New peptides, peptide-derived mimetics and anti-subdomain antibodies interact with specified subdomain sequences in the N domain of

carcinoembryonic antigen (CEA) and/or NCA involved in the differentiation-blocking activity associated with malignant tumors, releasing the CEA/NCA-imposed differentiation block so inducing the tumors to differentiate.

DETAILED DESCRIPTION - The subdomains consist of:

(i) sequences G30YSWYK; N42RQII; and Q80ND (where numbering begins

at

the first amino acid of the mature protein) and other sequences in the N terminal 107 amino acid domain of CEA; and

(ii) sequences in the internal A3B3 178 amino acid domain of CEA.

INDEPENDENT CLAIMS are also included for the following:

(1) agents useful in further methods of releasing the CEA/NCA-imposed differentiation block as follows:

(a) antisense oligonucleotides, antisense ribozymes or antisense cDNA

which hybridize to at least one domain of CEA/NCA mRNA sequences (optionally the subdomains above) and reduce CEA/NCA expression in tumors and metastases when administered to cancer patients; and

(b) 'shankless anchors', comprising the glycoposphatidyl-inositol (GPI) anchor of CEA without the external peptide domains, in which the

GPI

anchor interferes with downstream targets of endogenous CEA/NCA molecules to inhibit the differentiation-blocking activity of the endogenous

CEA/NCA

molecules when administered to cancer patients;

(2) a fourth method of inhibiting the differentiation-blocking activity of CEA/NCA molecules, comprising restoring endogenous **integrin** function (especially **integrins** alpha 5 beta 1 and alpha v beta 3) by administering **monoclonal** antibodies which reverse CEA/NCA-induced changes in **integrin** function then peptides/mimetics that mimic the effects of the **monoclonal** antibodies; and

(3) screening for agents inhibiting the signal processing required for differentiation-blocking activity of endogenous CEA/NCA, by screening for agents:

(a) releasing myogenic differentiation block in rat L6 myoblasts transfected to express CEA/NCA, and

(b) capable of restoring normal cellular and tissue architecture to human Caco-2 colonocytes aberrantly expressing high CEA/NCA levels.

ACTIVITY - Anti-tumor.

MECHANISM OF ACTION - Cancer cell differentiation stimulator. Cyclic peptides including sequences G30YSWYK, N42RQII or Q80ND, or **monoclonal** antibodies A20.12.2, were applied to L6 myoblasts producing CEA and released the CEA-imposed block in myogenic differentiation.

USE - The antibodies can be used in cancer therapy to release a block

on differentiation imposed by CEA/NCA in CEA/NCA-producing tumors and their metastases (claimed), so inducing them to differentiate and inhibiting their ability to grow; the peptides/mimetics, inhibiting antisense sequences and shankless anchor of (1) can similarly be used. Since CEA/NCA are believed to block differentiation by interfering with the function of **integrins**, the method of (2) can also be used in this way. The antibodies, peptides/mimetics, inhibiting antisense sequences and shankless anchors can also be used to enhance the efficacy

of other anti-cancer treatments, by increasing the differentiation status of the tumor and by enhancing the bystander effect, whereby more differentiated tumor cells cause adjacent tumor cells to behave more as non-malignant or normal cells (claimed). They can also be used to restore anoikis (**apoptosis** of cells not conforming to normal tissue architecture) and **apoptosis** to levels of non-malignant or normal cells, so increasing efficacy of all other cytotoxic chemotherapeutic drugs which depend on **apoptosis** for killing cells (claimed).

ADVANTAGE - Unlike prior art surgery, radiation or chemotherapy, the agents and methods are applicable to most human cancers and allow tumor cells to be specifically targeted, since most human cancers show up-regulation of CEA/NCA, whilst expression in normal cells is very limited.

Dwg.0/15

L35 ANSWER 26 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
 AN 1999-083565 [08] WPIDS  
 DNN N1999-060285 DNC C1999-025342  
 TI New human XAF genes which interact with inhibitors of **apoptosis** proteins - useful as diagnostic reagents and for prevention and treatment of **cancer**, neurodegenerative disorders and apoptotic conditions including HIV.  
 DC B04 D16 P14 S03  
 IN BAIRD, S; KORNELUK, R; LISTON, P; MACKENZIE, A E; TAMAI, K; KORNELUK, R G  
 PA (UYOT-N) UNIV OTTAWA; (APOP-N) APOPTOGEN INC  
 CYC 28  
 PI EP 892048 A2 19990120 (199908)\* EN 101p  
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT  
 RO SE SI  
 JP 11032780 A 19990209 (199916) 64p  
 CA 2225187 A 19990114 (199926)  
 US 6107088 A 20000822 (200042)  
 ADT EP 892048 A2 EP 1998-113003 19980713; JP 11032780 A JP 1997-252889  
 19970901; CA 2225187 A CA 1998-2225187 19980227; US 6107088 A Provisional  
 US 1997-52402 19970714, Provisional US 1997-54491 19970801, Provisional  
 US  
 1997-56338 19970818, US 1998-100391 19980619  
 PRAI US 1997-56338 19970818; US 1997-52402 19970714; US 1997-54491  
 19970801; US 1998-100391 19980619  
 AB EP 892048 A UPAB: 19990224  
 A substantially pure nucleic acid (I) encoding an XAF polypeptide (II), which interacts with inhibitors of **apoptosis** proteins (IAPs) and induce **apoptosis** is new. Also claimed are: (1) an antisense nucleic acid corresponding to at least 10 nucleotides of (I), able to decrease XAF biological activity; (2) a vector comprising (I), for XAF polypeptide expression; (3) a cell containing (I); (4) a transgenic animal generated from a cell genetically engineered to lack (I), unable to express (II); (5) an **antibody** for XAF polypeptide (II) or a fragment of (II); (6) methods for increasing **apoptosis** in a cell, comprising administering (i) XAF polypeptide (II); or (ii) a transgene encoding (II) or a fragment into a mammal cell; (7) a method of inhibiting **apoptosis** in a cell by administering a compound which decreases XAF biological activity; (8) methods for identifying a compound that modulates **apoptosis** by contacting a cell comprising: (i) a reporter gene operably linked to an XAF gene promoter; or (ii) a TRAF and an XAF polypeptide and a reporter gene operably linked to DNA comprising

an NF-kB binding site; or (iii) a TRAF, an **IAP** and an XAF polypeptide, and a reporter gene operably linked to DNA comprising an NF-kB binding site; with candidate compound and measuring change in expression; (9) methods for detecting **apoptosis** modulating compounds by exposing a cell having: (i) a reporter gene operably linked to a DNA-binding-protein recognition site (III); and (ii) a first XAF fusion gene (I) bonded to a binding moiety which binds (III); and (iii) a second XAF or **IAP** fusion protein with gene activating moieties; and measuring change in reporter gene expression; (10) a method as in

(9),

where the first fusion gene comprises an **IAP** polypeptide, and the second comprises XAF (II); and (11) methods for detecting **apoptosis** modulating compounds by: (i) immobilising an XAF polypeptide on a solid-phase substrate; (ii) contacting with an XAF or **IAP** polypeptide; (iii) adding the candidate compound, and measuring the binding; and (12) a method as (11), where the first polypeptide is **IAP**, and the second is XAF.

USE - The new XAF gene and its variants are useful for identifying compounds which modulate (increase or decrease) **apoptosis** by monitoring expression of XAF in the presence of a candidate (claimed). These compounds and XAF **antibodies** are useful for treating diseases related to overexpression of XAF (which causes **cell death**) e.g. neurodegenerative disorders, and activating compounds and XAF polypeptides can be administered to treat impaired **apoptosis** diseases caused by underexpression of XAF e.g. **cancer**. Gene therapy can also be used to treat the above conditions by administering the vector comprising an XAF gene (I) or the XAF antisense nucleic acid. Gene therapy or administration of XAF polypeptides are useful for preventing apoptotic conditions in patients with a degenerative disease, is HIV positive, or has a mutated XAF gene

or

aberrant XAF expression. The new XAF gene is useful for diagnosing a mammal with a disease related to altered **apoptosis** expression by determining the presence of a gene mutation, or measuring gene activity levels (claimed). The XAF expressing cells are useful for studies of XAF genes and gene products, especially for identifying domains of biological activity, and for production of large amounts of normal and mutant protein. XAF **antibodies** are useful for detecting XAF proteins, and are useful in therapeutic treatments by inhibiting the biological activity of the proteins, or coupling to active compounds for targeting

to

specific tissues. XAF nucleic acids are useful for identifying homologous clones and sequences using low stringency hybridisation.

L35	ANSWER 27 OF 37	USPATFULL	DUPLICATE 3
AN	1998:153860	USPATFULL	
TI	Restoration of normal phenotype in cancer cells		
IN	Bissell, Mina J., Berkeley, CA, United States		
	Weaver, Valerie M., Oakland, CA, United States		
PA	The Regents of the University of California, Oakland, CA, United States (U.S. corporation)		
PI	US 5846536	19981208	
AI	US 1996-726230	19961004 (8)	
DT	Utility		
EXNAM	Primary Examiner: Feisee, Lila; Assistant Examiner: Bansal, Geetha P.		
LREP	Martin, Paul R.; Ross, Pepi		
CLMN	Number of Claims: 8		

ECL Exemplary Claim: 1  
 DRWN 14 Drawing Figure(s); 6 Drawing Page(s)  
 LN.CNT 1002  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB A method for reversing expression of malignant phenotype in cancer cells

is described. The method comprises applying .beta..sub.1  
**integrin** function-blocking **antibody** to the cells. The  
 method can be used to assess the progress of cancer therapy. Human  
 breast epithelial cells were shown to be particularly responsive.

L35 ANSWER 28 OF 37 USPATFULL  
 AN 1998:138709 USPATFULL  
 TI Regulated **apoptosis**  
 IN Crabtree, Gerald R., Woodside, CA, United States  
 Schreiber, Stuart L., Cambridge, MA, United States  
 Spencer, David M., Los Altos, CA, United States  
 Wandless, Thomas J., Cambridge, MA, United States  
 Belshaw, Peter, Somerville, MA, United States  
 PA President & Fellows of Harvard College, Cambridge, MA, United States  
 (U.S. corporation)  
 Board of Trustees of Leland Stanford Jr. University, Stanford, CA,  
 United States (U.S. corporation)  
 PI US 5834266 19981110  
 AI US 1994-292597 19940818 (8)  
 RLI Continuation-in-part of Ser. No. US 1994-179143, filed on 7 Jan 1994,  
 now abandoned And Ser. No. US 1994-179748, filed on 7 Jan 1994 which is  
 a continuation-in-part of Ser. No. US 1993-92977, filed on 16 Jul 1993,  
 now abandoned which is a continuation-in-part of Ser. No. US  
 1993-17931,  
 filed on 12 Feb 1993, now abandoned , said Ser. No. US 179143 which is  
 a  
 continuation-in-part of Ser. No. US 1993-93499, filed on 16 Jul 1993  
 DT Utility  
 EXNAM Primary Examiner: Elliott, George C.; Assistant Examiner: Schwartzman,  
 Robert  
 LREP Vincent, Matthew P.; Clauss, Isabelle M.Foley, Hoag & Eliot LLP  
 CLMN Number of Claims: 235  
 ECL Exemplary Claim: 118  
 DRWN 35 Drawing Figure(s); 34 Drawing Page(s)  
 LN.CNT 5299  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB We have developed a general procedure for the regulated (inducible)  
 dimerization or oligomerization of intracellular proteins and disclose  
 methods and materials for using that procedure to regulatably initiate  
 cell-specific **apoptosis** (programmed **cell**  
**death**) in genetically engineered cells.

L35 ANSWER 29 OF 37 USPATFULL  
 AN 1998:7052 USPATFULL  
 TI Combination of necrosis-inducing substances with substances which are  
 activated by necroses for the selective therapy of tumors and  
 inflammatory disorders  
 IN Bosslet, Klaus, Marburg, Germany, Federal Republic of  
 Czech, Jorg, Marburg, Germany, Federal Republic of  
 Hoffmann, Dieter, Marburg-Elnhausen, Germany, Federal Republic of  
 PA Behringwerke Aktiengesellschaft, Marburg, Germany, Federal Republic of

(non-U.S. corporation)  
 PI US 5710134 19980120  
 AI US 1995-446211 19950519 (8)  
 PRAI DE 1994-4417865 19940520  
 DT Utility  
 EXNAM Primary Examiner: Reamer, James H.  
 LREP Foley & Lardner  
 CLMN Number of Claims: 14  
 ECL Exemplary Claim: 1  
 DRWN No Drawings  
 LN.CNT 475  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
 AB The invention relates to a combination of substances (component I) inducing necrosis in tumors or inflamed tissue with other nontoxic substances ("prodrugs", component II). The enzymes set free by necrotic processes then cleave the nontoxic "prodrug" into the toxic "drug", which leads to massive tumor **cell death** and/or remission of inflammation.

L35 ANSWER 30 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
 AN 1999-095328 [08] WPIDS  
 DNC C1999-028074  
 TI New isolated Rac-guanine nucleotide exchange factor - used to develop products for treating conditions involving e.g. cell proliferation (e.g. **cancer**), programmed **cell death**, haemostasis or bone resorption.  
 DC B04 D16  
 IN BOLLAG, G; CROMPTON, A; NORTH, A; ROSCOE, W; SHARMA, S  
 PA (ONYX-N) ONYX PHARM INC  
 CYC 80  
 PI WO 9857990 A2 19981223 (199908)\* EN 61p  
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
 OA PT SD SE SZ UG ZW  
 W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE  
 GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW  
 MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU  
 ZW  
 AU 9879664 A 19990104 (199921)  
 EP 996638 A2 20000503 (200026) EN  
 R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE  
 CN 1268954 A 20001004 (200067)  
 ADT WO 9857990 A2 WO 1998-US12391 19980615; AU 9879664 A AU 1998-79664 19980615; EP 996638 A2 EP 1998-930220 19980615, WO 1998-US12391 19980615; CN 1268954 A CN 1998-805926 19980615  
 FDT AU 9879664 A Based on WO 9857990; EP 996638 A2 Based on WO 9857990  
 PRAI US 1997-49879 19970617  
 AB WO 9857990 A UPAB: 19990302  
 An isolated Rac-guanine nucleotide exchange factor (GEF) polypeptide and biologically active fragments are new. Also claimed are: (1) an isolated nucleic acid comprising a nucleotide sequence (NS) coding for a Rac-GEF polypeptide; (2) an isolated nucleic acid comprising a NS which hybridises, or whose nucleic acid complement hybridises, under stringent conditions to base pairs of NS 900-1482 in sequence (I) of 3171 nucleotides in length; (3) an isolated nucleic acid comprising a NS which is unique to Rac-GEF; (4) an isolated nucleic acid comprising a NS which hybridises, or whose nucleic acid complement hybridises, under stringent conditions to a unique NS as in (3); (5) a transformed host cell

containing a nucleic acid as in (1) or (2); (6) a vector comprising a nucleic acid as in (1) or (2); (7) a method of isolating a molecule that binds to a guanine nucleotide-depleted state of a Rac polypeptide comprising: (a) contacting a Rac polypeptide with a medium comprising the molecule for the molecule to bind to the Rac polypeptide; and (b) separating the Rac polypeptide to which the molecule has bound from the medium; (8) a method of modulating an activity of a GTPase comprising administering a GEF or a biologically-active fragment, or a compound

which

modulates the activity of the GEF; (9) a method of testing for an agent which modulates the guanine nucleotide exchange activity of a GEF comprising: (a) contacting a mixture of a polypeptide comprising a GEF,

or

a biologically-active fragment, and a polypeptide comprising a GTPase, or a biologically-active fragment, to which the exchange factor can bind, with an agent; and (b) assaying for the presence or amount of guanine nucleotide exchange activity in the presence or absence of a GEF

enhancer;

(10) a method of testing for an agent which modulates the binding between a GEF and a GTPase comprising: (a) as in (9a); (b) detecting the presence or amount of binding between the GEF polypeptide, or the biologically-active fragment, and the GTPase; (11) a method of increasing the guanine nucleotide exchange activity of a GEF, or a biologically-active fragment, the factor capable of acting on a member of the Ras superfamily of GTPases, comprising: (a) contacting the GEF, or a biologically-active fragment with the member of the Ras superfamily of GTPases, or a biologically-active fragment; and (b) assaying for guanine nucleotide exchange activity in the presence of a GEF enhancer; (12) an isolated **antibody** which is specific for a Rac-GEF or a peptide comprising a sequence present in Rac-GEF, and (13) ligands that bind to the Src homology domain on Rac-GEF.

USE - The Rac-GEF polypeptides have specific binding affinity for a guanine nucleotide-depleted state of G-proteins (in particular Rac), a guanine nucleotide exchange activity, an oncogenic transforming activity, and an immunogenic activity. The products can be used in the regulation

of

biological pathways in which a GTPase is involved, particularly pathological conditions, e.g. cell proliferation (e.g. **cancer**), growth control, morphogenesis, stress fibre formation, and **integrin**-mediated interactions such as embryonic development, **tumour** cell growth and metastasis, programmed **cell death**, haemostasis, **leukocyte** homing and activation, bone resorption, clot retraction, and the response of cells to mechanical stress. In particular, the products can be used for treating e.g. **cancer**, diseases associated with abnormal cell proliferation, diseases associated with inflammation, and/or the chemotactic ability of neutrophils. The products can also be used for detection, diagnosis and production of transgenic animals.

Dwg.0/6

L35 ANSWER 31 OF 37 USPATFULL

AN 97:112162 USPATFULL

TI Enhanced intercellular interaction by associational **antibody** molecules

IN Creekmore, Stephen P., Frederick, MD, United States  
Hecht, Toby T., Bethesda, MD, United States  
Ortaldo, John, Frederick, MD, United States

PA The United States of America as represented by the Department of Health  
and Human Services, Washington, DC, United States (U.S. government)  
PI US 5693322 19971202  
AI US 1993-30843 19930311 (8)  
DT Utility  
EXNAM Primary Examiner: Scheiner, Toni R.  
LREP Knobbe, Martens, Olson & Bear LLP  
CLMN Number of Claims: 28  
ECL Exemplary Claim: 1  
DRWN 16 Drawing Figure(s); 7 Drawing Page(s)  
LN.CNT 1471

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method to enhance intercellular association between two or more cells  
through the linking of attachment molecules on the cellular surfaces of  
the cells is described. Appropriate attachment molecules include  
**antibodies** having an IgG.sub.3 isotype that can cross-associate  
with **antibodies** on other cells to bring the cells into  
proximity with one another. An enhanced method to kill tumor cells with  
effector cells is also provided.

L35 ANSWER 32 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 1997-457317 [42] WPIDS

DNN N1997-380895 DNC C1997-145968

TI Screening for **apoptosis** inducers such as **antibodies**,  
for use as anticancer agents - by use of cells expressing  
**integrin**-associated protein as screen.

DC B04 D16 S03

IN FUKUSHIMA, N

PA (CHUS) CHUGAI SEIYAKU KK; (CHUS) CHUGAI PHARM CO LTD

CYC 76

PI WO 9732601 A1 19970912 (199742)\* JA 46p  
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT  
SD SE SZ UG  
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE  
GH HU IL IS KE KG KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO  
NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN YU

AU 9722325 A 19970922 (199804)

JP 09295999 A 19971118 (199805) 14p

EP 903149 A1 19990324 (199916) EN

R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

ADT WO 9732601 A1 WO 1997-JP702 19970306; AU 9722325 A AU 1997-22325  
19970306;

JP 09295999 A JP 1997-67499 19970306; EP 903149 A1 EP 1997-906844  
19970306, WO 1997-JP702 19970306

FDT AU 9722325 A Based on WO 9732601; EP 903149 A1 Based on WO 9732601

PRAI JP 1996-78182 19960306

AB WO 9732601 A UPAB: 19971021

A screen for substances which induce **apoptosis**, consists of the  
use of cells which express **integrin**-associated protein (  
**IAP**), such as **myelocytes**, as the cells in which  
**apoptosis** is induced.

Also claimed are **apoptosis**-inducers (such as  
**antibodies**) identified by the method above, which bind to  
**IAP**, and drug compositions containing them.

USE - The process is used for the simple and efficient screening of  
potential anticancer agents, especially for the treatment of  
**myelocytic** leukaemia.

Dwg.6/17

L35 ANSWER 33 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD  
 AN 1997-385335 [35] WPIDS  
 DNN N1997-320755 DNC C1997-123609  
 TI New neuronal inhibitor of **apoptosis** - useful for diagnosing and  
 treating, e.g. **cancer**, AIDS or amyotrophic lateral sclerosis.  
 DC B04 D16 P14 S03  
 IN KORNELUK, R G; MACKENZIE, A E; ROBERTSON, G; ROY, N; TAMAI, K  
 PA (UYOT-N) UNIV OTTAWA  
 CYC 73  
 PI WO 9726331 A2 19970724 (199735)\* EN 102p  
 RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD  
 SE SZ UG  
 W: AL AM AT AU AZ BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE HU  
 IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ  
 PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN  
 AU 9716149 A 19970811 (199747)  
 EP 815231 A1 19980107 (199806) EN  
 R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE  
 WO 9726331 A3 19971002 (199814)  
 JP 11503620 W 19990330 (199923) 150p  
 ADT WO 9726331 A2 WO 1997-IB142 19970117; AU 9716149 A AU 1997-16149  
 19970117;  
 EP 815231 A1 EP 1997-902522 19970117, WO 1997-IB142 19970117; WO 9726331  
 A3 WO 1997-IB142 19970117; JP 11503620 W JP 1997-525841 19970117, WO  
 1997-IB142 19970117  
 FDT AU 9716149 A Based on WO 9726331; EP 815231 A1 Based on WO 9726331; JP  
 11503620 W Based on WO 9726331  
 PRAI GB 1996-1108 19960119  
 AB WO 9726331 A UPAB: 19970828  
 A new method for inhibiting **apoptosis** in a cell comprises  
 administering to cells: (a) a NAIP (neuronal inhibitor of  
**apoptosis** protein) polypeptide; (b) a transgene expressing NAIP;  
 or its fragments; or (c) a compound (A) that increases biological  
 activity  
 of NAIP.  
 Also new are: (1) methods for increasing or inducing  
**apoptosis** by administering a compound that decreases NAIP  
 activity; (2) a purified nucleic acid (I) encoding (NAIP); (3) vectors,  
 host cells and transgenic animals containing (I); (4) purified NAIP and  
 its fragments; (5) **antibodies** (Ab) that bind to (NAIP); (6) a  
 method for identifying modulators of **apoptosis** comprising: (a)  
 providing a cell expressing a NAIP polypeptide; and (b) contracting the  
 cell with a candidate compound and monitoring the expression of the NAIP  
 gene; (7) a method for treatment of SMA by administration of a  
 polypeptide  
 (or nucleic acid encoding it) having at least two BIR (baculovirus  
**IAP** repeat) domains of an anti-apoptotic protein.  
 USE - The methods are applied to mammalian, especially human cells,  
 particularly in patients who are HIV-positive or have AIDS; a  
 neurodegenerative disease; myelodysplastic syndrome or ischaemic injury  
 (e.g. myocardial infarction, stroke, reperfusion injury, renal failure  
 etc.). Fragments of (IV) can be used as primers or probes to identify or  
 detect NAIP genes (which are associated with spinal muscular atrophy) in  
 cells, e.g. to diagnose conditions involving altered levels of  
**apoptosis**, specifically amyotrophic lateral sclerosis but also

many different sorts of **cancer**, also to isolate related NAIP genes. (IV) is used to produce recombinant (I). Diseases involving altered

levels of **apoptosis** (or predisposition to such diseases) are diagnosed by detecting a mutation in the NAIP gene or by measuring NAIP gene expression (from the level of protein or mRNA) in comparison with normal control cells. Ab are used to detect (including by imaging), quantify or purify NAIP, or therapeutically to inhibit NAIP, hence promote

**apoptosis.**

Dwg.0/7

L35 ANSWER 34 OF 37 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 1997-350966 [32] WPIDS

DNC C1997-113367

TI Isolated protein homologues of viral inhibitors of **apoptosis** - used to modulate **apoptosis** for treatment of degenerative, infectious or auto immune diseases and **cancer**.

DC B04 D16

IN VAUX, D L

PA (AMRA-N) AMRAD OPERATIONS PTY LTD

CYC 75

PI WO 9723501 A1 19970703 (199732)\* EN 136p

RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD  
SE SZ UG

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE  
HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX  
NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN

AU 9710891 A 19970717 (199745)

EP 868430 A1 19981007 (199844) EN

R: AL AT BE CH DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT RO SE  
SI

AU 710221 B 19990916 (199950)

JP 2000504932 W 20000425 (200031) 133p

ADT WO 9723501 A1 WO 1996-AU827 19961220; AU 9710891 A AU 1997-10891

19961220;

EP 868430 A1 EP 1996-941537 19961220, WO 1996-AU827 19961220; AU 710221 B

AU 1997-10891 19961220; JP 2000504932 W WO 1996-AU827 19961220, JP

1997-523157 19961220

FDT AU 9710891 A Based on WO 9723501; EP 868430 A1 Based on WO 9723501; AU 710221 B Previous Publ. AU 9710891, Based on WO 9723501; JP 2000504932 W Based on WO 9723501

PRAI AU 1995-7275 19951222

AB WO 9723501 A UPAB: 19970806

Isolated protein (A), comprising a cell-derived homologue of a viral inhibitor of **apoptosis** (IAP), or its derivative or chemical analogue, able to inhibit apoptotic response in cells to viral infection is new. Also new are isolated nucleic acid molecules (I) encoding (A).

USE - (A) are used to modulate (both promote or inhibit) **apoptosis** in animal cells, specifically for treatment, by inhibition, of degenerative or infectious diseases (e.g. Alzheimer's or motor neuron disease, stroke and myocardial infarction, or AIDS), or, by promotion, **cancer** and autoimmune disease (claimed). (I) may be used for gene therapy of these diseases. **Antibodies** against (A) are useful in diagnostic assays, e.g. to detect **cancer** (or predisposition to it) and for monitoring treatment, to screen for

IAP homologues and to purify (A). Also, (A) are useful for detecting specific **antibodies**, e.g. in certain autoimmune diseases.

L35 ANSWER 35 OF 37 HCAPLUS COPYRIGHT 2001 ACS  
 AN 1997:349934 HCAPLUS  
 DN 127:80045  
 TI Multiple systems for recognition of apoptotic **lymphocytes** by macrophages  
 AU Pradhan, Deepti; Krahling, Stephen; Williamson, Patrick; Schlegel, Robert A.  
 CS Department of Biochemistry and Molecular Biology, Pennsylvania State University, University Park, PA, 16802, USA  
 SO Mol. Biol. Cell (1997), 8(5), 767-778  
 CODEN: MBCEEV; ISSN: 1059-1524  
 PB American Society for Cell Biology  
 DT Journal  
 LA English  
 AB In vivo, apoptotic lymphocytes are recognized and phagocytosed by macrophages well before the final stages of DNA degradn. and cell lysis. The recognition process is apparently triggered by the exposure of phosphatidylserine (PS) on the cell surface, an event which precedes cell lysis by several hours. However, multiple receptors appear to respond to this event. The authors demonstrate here that both activated and unactivated macrophages recognize PS, but with different receptor systems.  
 Phagocytosis of apoptotic lymphocytes by activated (but not by unactivated) macrophages is inhibited by pure PS vesicles as well as by N-acetylglucosamine, implicating involvement of a lectin-like receptor in this case. Conversely, uptake of apoptotic lymphocytes by unactivated (but not by activated) macrophages is inhibited by PS on the surface of erythrocytes as well as by the tetrapeptide RGDS and cationic amino acids and sugars, implicating involvement of the vitronectin receptor in this case. Recognition by both classes of macrophages is blocked by the monocyte-specific monoclonal antibody 61D3. The signal recognized by activated macrophages appears to develop on the lymphocyte prior to assembly of the signal recognized by unactivated macrophages. Collectively, these results suggest that PS exposure on the surface of apoptotic lymphocytes generates a complex and evolving signal recognized by different receptor complexes on activated and unactivated macrophages.

L35 ANSWER 36 OF 37 USPATFULL  
 AN 95:1370 USPATFULL  
 TI Modulation of inflammatory responses by administration of GMP-140 or **antibody** to GMP-140  
 IN McEver, Rodger P., Oklahoma City, OK, United States  
 PA Board of Regents of the University of Oklahoma, Norman, OK, United States (U.S. corporation)  
 PI US 5378464 19950103  
 AI US 1989-320408 19890308 (7)  
 DT Utility  
 EXNAM Primary Examiner: Walsh, Stephen G.  
 LREP Kilpatrick & Cody  
 CLMN Number of Claims: 9  
 ECL Exemplary Claim: 1  
 DRWN 6 Drawing Figure(s); 6 Drawing Page(s)  
 LN.CNT 1387

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method using compounds inhibiting binding reactions involving GMP-140 to modulate an inflammatory response. The method is based on the discovery that GMP-140, released from the storage granules of platelets, endothelial cells, and megakaryocytes, and redistributed to the surface of the cells within seconds of activation by mediators such as thrombin, ionophores or histamine, binds to a ligand on neutrophils, and the plasma proteins C3b and protein S. Adhesion of the cells following activation is blocked directly by administration of **antibody** to GMP-140 or its ligand, or by competitive inhibition by administration of soluble GMP-140, the GMP-140 ligand, or the specific carbohydrate portion of the ligand bound by GMP-140.

L35 ANSWER 37 OF 37 HCAPLUS COPYRIGHT 2001 ACS

AN 1995:204275 HCAPLUS

DN 122:7710

TI Recognition of apoptotic cells by human macrophages: inhibition by a **monocyte**/macrophage-specific **monoclonal** antibody

AU Flora, Pauline K.; Gregory, Christopher D.

CS Med. Sch., Univ. Birmingham, Birmingham, UK

SO Eur. J. Immunol. (1994), 24(11), 2625-32

CODEN: EJIMAF; ISSN: 0014-2980

DT Journal

LA English

AB Cells undergoing death by apoptosis are rapidly engulfed by phagocytes in vivo, a highly efficient process which prevents leakage of potentially dangerous intracellular contents from dying cells to neighboring tissue. A panel of monoclonal antibodies (mAb) specifying a range of human monocyte/macrophage surface antigens were tested for their capacity to inhibit the in vitro recognition of apoptotic cells by human peripheral blood monocyte-derived macrophages. The results identify the antigen defined by the 61D3 mAb, a widely-used marker of monocyte/macrophage lineage cells, as an important mediator of apoptotic cell recognition.

In this system, apoptotic, but not viable cells were recognized by the cultured macrophages and 61D3 was found to inhibit the recognition of all apoptotic cell types tested, including Ca<sup>2+</sup> ionophore-treated or growth factor-depleted B and T lymphocyte lines, tonsillar germinal center B cells, irradiated peripheral blood lymphocytes and senescing neutrophils. Furthermore, the apoptotic cell recognition pathway specified by 61D3 could be distinguished from that involving the macrophage .alpha.v.beta.3 vitronectin receptor which has been shown previously to play an important role in the recognition of apoptotic cells. These results provide further evidence that the mechanisms underlying rapid clearance of apoptotic cells involve multiple phagocyte receptors.

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FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 17 January 2001 (20010117/ED)

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for details.

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DEL HIS Y

FILE 'BIOSIS' ENTERED AT 10:10:29 ON 18 JAN 2001  
L1 69769 S APOPTOSIS OR CELL (3A) DEATH  
L2 145631 S MONOCLONAL#  
L3 18090 S INTEGRIN# OR IAP#  
L4 45 S L1 AND L2 AND L3  
L5 1577766 S BLOOD# OR LYMPH? OR MYELOCYT? OR LEUKEMIA OR MONOCYT? OR  
LEUK  
L6 26 S L4 AND L5

FILE 'BIOSIS' ENTERED AT 10:13:03 ON 18 JAN 2001

=> d bib ab 1-26

L6 ANSWER 1 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS  
AN 2000:280086 BIOSIS  
DN PREV200000280086  
TI Interleukin-11 enhancement of VLA-5 mediated adhesion of CD34+ cells from  
cord **blood** to fibronectin is associated with the PI-3 kinase  
pathway.  
AU Wang, Li-Sheng; Liu, Hong-Jun; Broxmeyer, Hal. E.; Lu, Li  
SO In Vivo (Attiki), (March April, 2000) Vol. 14, No. 2, pp. 331-338.  
print..  
ISSN: 0258-851X.  
DT Article  
LA English  
SL English  
AB Adhesion is required for cell growth, differentiation, survival, and  
function. Cell adhesion is mediated by a structurally diverse group of  
plasma membrane receptors, each exhibiting specialized ligand-binding  
properties that are needed for specific tasks. Intergrin-mediated  
adhesion  
is important for hematopoietic stem (HSC)/progenitor (HPC) cell survival  
and may prevent programmed **cell death**. Interleukin  
(IL)-11, a multi-functional cytokine secreted by the bone marrow  
environment, plays an important role in regulating growth and

differentiation of HSCs/HPCs. In this report, we demonstrate that IL-11 enhanced adhesion of freshly isolated and 3 day-expanded CD34+ cells to immobilized fibronectin. The expression of very late antigen (VLA)-4 and VLA-5 **integrins** was detected on CD34+ cells. CD34+ cells also expressed  $\alpha$ -chain and gp130 subunits of the IL-11 receptor (R). Enhanced adhesion by IL-11 was mediated via activation of VLA-5 **integrins**, since this action could be blocked by **monoclonal** antibodies against  $\beta$ 1 and  $\alpha$ 5, but not  $\alpha$ 4, **integrins**. Addition of phosphatidylinositol (PI) -3 kinase inhibitors blocked IL-11 enhanced adhesion of CD34+ cells to fibronectin. The results suggest that this enhanced adhesion is associated with the PI-3 kinase pathway, an inside-out signaling pathway.

L6 ANSWER 2 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS

AN 2000:278119 BIOSIS

DN PREV200000278119

TI Molecular characterization of the surface of apoptotic neutrophils:  
Implications for functional downregulation and recognition by phagocytes.

AU Hart, S. P.; Ross, J. A.; Ross, K.; Haslett, C.; Dransfield, I.

SO Cell Death and Differentiation, (May, 2000) Vol. 7, No. 5, pp. 493-503.  
print..  
ISSN: 1350-9047.

DT Article

LA English

SL English

AB We have used a panel of **monoclonal** antibodies and lectins to examine the profile of surface molecule expression on human neutrophils that have undergone spontaneous **apoptosis** during in vitro culture. Neutrophil **apoptosis** was found to be accompanied by down-regulation of the immunoglobulin superfamily members PECAM-1 (CD31), ICAM-3 (CD50), CD66acde, and CD66b and the **integrin**-associated proteins CD63 and urokinase plasminogen activator receptor (CD87) that

may alter the potential for adhesive interactions. Cellular interactions may be further influenced by the reduction of the expression of surface carbohydrate moieties, including sialic acid. Reduced expression of Fc $\gamma$ RIII (CD32), complement receptor type 1 (CD35) and receptors for pro-inflammatory mediators C5a (CD88) and TNF $\alpha$  (CD120b) associated with **apoptosis** might limit neutrophil responsiveness to stimuli that trigger degranulation responses. Although many of the receptors we have examined are expressed at reduced levels on apoptotic neutrophils,

we found that there was differential loss of certain receptors (e.g. CD16, CD15 and CD120b) and increased expression of aminopeptidase-N (CD13). Together with our previous data showing that expression of certain molecules e.g. LFA-3 (CD58) is not altered during neutrophil **apoptosis**, these data are suggestive of specific changes in receptor mobilisation and shedding associated with **apoptosis**. Although reduced expression of CD63 (azurophilic granules) and CR1 (specific granules) indicates that granule mobilisation does not

accompany **apoptosis**, a **monoclonal** antibody (BOB78), that recognises a 90 kDa antigen localised in intracellular granules, defines

a subpopulation of apoptotic neutrophils that exhibit nuclear degradation yet retain intact plasma membranes. BOB78 positive neutrophils were found

to bind biotinylated thrombospondin, suggesting that this mAb defines surface molecular changes associated with exposure of thrombospondin binding moieties.

L6 ANSWER 3 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS  
 AN 2000:191821 BIOSIS  
 DN PREV200000191821  
 TI Engagement of the alpha2beta1 **integrin** inhibits Fas ligand expression and activation-induced **cell death** in T cells in a focal adhesion kinase-dependent manner.  
 AU Aoudjit, Fawzi; Vuori, Kristiina (1)  
 CS (1) Cancer Research Center, Burnham Institute, 10901 N Torrey Pines Rd, La Jolla, CA, 92037 USA  
 SO Blood, (March 15, 2000) Vol. 95, No. 6, pp. 2044-2051. ISSN: 0006-4971.  
 DT Article  
 LA English  
 SL English  
 AB T-cell receptor (TCR)-mediated **apoptosis**, also known as activation-induced **cell death** (AICD), plays an important role in the control of immune response and in the development of T-cell repertoire. Mechanistically, AICD has been largely attributed to the interaction of Fas ligand (Fas-L) with its cell surface receptor Fas in activated T cells. Signal transduction mediated by the **integrin** family of cell adhesion receptors has been previously shown to modulate **apoptosis** in a number of different cell types; in T cells, **integrin** signaling is known to be important in cellular response to antigenic challenge by providing a co-stimulatory signal for TCR. In this study we demonstrate that signaling via the collagen receptor alpha2beta1 **integrin** specifically inhibits AICD by inhibiting Fas-L expression in activated Jurkat T cells. Engagement of the alpha2beta1 **integrin** with **monoclonal** antibodies or with type I collagen, a cognate ligand for alpha2beta1, reduced anti-CD3 and PMA/ionomycin-induced **cell death** by 30% and 40%, respectively, and the expression of Fas-L mRNA by 50%. Further studies indicated that the alpha2beta1-mediated inhibition of AICD and Fas-L expression required the focal adhesion kinase FAK, a known component in the **integrin** signaling pathways. These results suggest a role for the alpha2beta1 **integrin** in the control of homeostasis of immune response and T-cell development.

L6 ANSWER 4 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS  
 AN 2000:128542 BIOSIS  
 DN PREV200000128542  
 TI Role of beta2 **integrins** in the prevention of **apoptosis** induction in chronic **lymphocytic leukemia** B cells.  
 AU Plate, J. M. D. (1); Long, B. W.; Kelkar, S. B.  
 CS (1) Section of Medical Oncology, Rush-Presbyterian St Luke's Medical Center, 1653 West Congress Parkway, Chicago, IL, 60612 USA  
 SO Leukemia (Basingstoke), (Jan., 2000) Vol. 14, No. 1, pp. 34-39. ISSN: 0887-6924.  
 DT Article  
 LA English  
 SL English  
 AB Immunologically committed **lymphocytes**, especially mature,

leukemic B cells, proliferate then accumulate without further cell division in chronic **lymphocytic leukemia** patients (CLL). These mature, leukemic B cells often produce autoantibodies. Under normal circumstances, immunologically committed **lymphocytes** that are autoreactive are deleted by a programmed **cell death** mechanism. In CLL cells, these mechanisms appear to be inhibited; therefore, cells accumulate rather than be destroyed. To understand the mechanism by which cell survival is selected over death in CLL cells, we studied the role of beta2 **integrins** and their ligands in the regulation of **apoptosis**. CLL cells were treated with **monoclonal** antibodies directed against beta2 **integrins**. Antibodies directed against the I-domain of the alpha chain of CD11b/CD18 inhibited **apoptosis**. The identity of the physiological ligand or counter-receptor for beta2 **integrins** that was required for the inhibition of **apoptosis** induction was sought. The ligand iC3b, but not ICAM-1 or fibrinogen, was identified as a ligand that could prevent **apoptosis** of CLL B cells. Free iC3b levels were elevated in CLL patients indicating that this ligand is available in vivo where it may interact with beta2 **integrins** on CLL B cells and sustain their viability by preventing activation of the programmed **cell death** pathway.

L6 ANSWER 5 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS

AN 2000:121633 BIOSIS

DN PREV200000121633

TI Antibody engagement of intercellular adhesion molecule 3 triggers **apoptosis** of normal and leukaemic myeloid marrow cells.

AU Stucki, Anne; Hayflick, Joel S. (1); Sandmaier, Brenda M.

CS (1) ICOS Corporation, 22021 20th Avenue SE, Bothell, WA, 98021 USA

SO British Journal of Haematology, (Jan., 2000) Vol. 108, No. 1, pp. 157-166.

ISSN: 0007-1048.

DT Article

LA English

SL English

AB Intercellular adhesion molecule 3 (ICAM-3, CD50) is an immunoglobulin (Ig)

domain-containing cell-cell adhesion receptor that binds to the **lymphocyte** function antigen 1 (LFA-1; CD11a/CD18) **integrin**. It is constitutively expressed on haematopoietic precursors and differentiated leucocytes, as well as on most leukaemic cells. ICAM-3/LFA-1 binding during a **lymphocyte**-mediated cellular immune response has been well established; however, its role in the

marrow

compartment is unclear. In this study, marrow cells from normal and acute leukaemic donors, as well as leukaemic cell lines, were cultured in the presence of various **monoclonal** antibodies (mAbs) to ICAM-3, and **apoptosis** was subsequently measured by annexin V binding. Anti-ICAM-3 mAb ICR 1.1 engagement triggered increased percentages of **apoptosis** among normal and leukaemic marrow myeloid cells. Fab fragments of ICR 1.1 mimicked the intact mAb, suggesting that the apoptotic signal was independent of Fc receptor interactions and did not require bivalent epitope engagement. In addition, the apoptotic signal

was

found to be independent of ICAM-1/LFA-1 binding interactions, as well as Fas/FasL and tumour necrosis factor alpha (TNF-alpha)/TNF receptor-activated pathways, as neutralizing antibodies to CD11a/CD18,

Fas

and TNF-alpha failed to abrogate the response.

- L6 ANSWER 6 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS  
 AN 2000:46215 BIOSIS  
 DN PREV200000046215  
 TI **Apoptosis** of bone marrow cells via **integrin** associated protein by the novel **monoclonal** antibody.  
 AU Fukushima, N. (1); Uno, S. (1); Tamura, M. (1); Matsuzaki, J. (1)  
 CS (1) Fuji Gotemba Labs Chugai Pharmaceutical Co., LTD., Gotemba-city, Shizuoka Japan  
 SO Blood, (Nov. 15, 1999) Vol. 94, No. 10 SUPPL. 1 PART 1, pp. 479a. Meeting Info.: Forty-first Annual Meeting of the American Society of Hematology New Orleans, Louisiana, USA December 3-7, 1999 The American Society of Hematology  
 . ISSN: 0006-4971.  
 DT Conference  
 LA English
- L6 ANSWER 7 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS  
 AN 2000:12012 BIOSIS  
 DN PREV200000012012  
 TI Correlation of cell proliferation inhibition and **apoptosis** induction with expression of human beta5 **integrin** on hematopoietic cells.  
 AU Yin Lianhua (1); Fu Siqing; Zhao Xinyong (1); Garcia-Sanchez, Felix; Deisseroth, Albert B.  
 CS (1) Department of Pathophysiology, Shanghai Medical University, Shanghai, 200032 China  
 SO Chinese Medical Journal (English Edition), (July, 1999) Vol. 112, No. 7, pp. 659-664.  
 ISSN: 0366-6999.  
 DT Article  
 LA English  
 SL English  
 AB Objective: To investigate the function of the alphavbeta5 **integrin** in hematopoietic cells. Methods: Tissue culture, **integrin** expression vectors, gene transfer, polymerase chain reaction (PCR), **apoptosis** analyses and cytometric analysis were made on hematopoietic cells. Results: The beta5 **integrin** cDNA was not expressed in hematopoietic cells following exposure to the beta5 **integrin** retrovirus vector pGbeta5CHT. Unbalanced expression of the alphavbeta3 and alphavbeta5 **integrins** occurred during **apoptosis** induced by serum depletion and upon differentiation. The treatment of hematopoietic cells with anti-alphavbeta5 **monoclonal** antibody inhibited **apoptosis** induced by serum depletion. Inducible expression of the beta5 **integrin** cDNA in the hematopoietic cell line K562 caused cellular proliferation inhibition. Conclusion: The alphavbeta5 **integrin** cDNA in hematopoietic cells can inhibit the proliferation of the hematopoietic cell, cause the differentiation of the hematopoietic cells and induce the **apoptosis** of the hematopoietic cells.
- L6 ANSWER 8 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS  
 AN 1999:523250 BIOSIS  
 DN PREV199900523250  
 TI Resting and cytokine-stimulated human small airway epithelial cells recognize and engulf apoptotic eosinophils.

AU Walsh, Garry M. (1); Sexton, Darren W.; Blaylock, Morgan G.; Convery, Catherine M.  
 CS (1) Department of Medicine and Therapeutics, University of Aberdeen, Foresterhill, IMS Building, Aberdeen, AB25 2ZD UK  
 SO Blood, (Oct. 15, 1999) Vol. 94, No. 8, pp. 2827-2835.  
 ISSN: 0006-4971.  
 DT Article  
 LA English  
 SL English  
 AB Eosinophils, which are prominent cells in asthmatic inflammation, undergo **apoptosis** and are recognized and engulfed by phagocytic macrophages in vitro. We have examined the ability of human small airway epithelial cells (SAEC) to recognize and ingest apoptotic human eosinophils. Cultured SAEC ingested apoptotic eosinophils but not freshly isolated eosinophils or opsonized erythrocytes. The ability of SAEC to ingest apoptotic eosinophils was enhanced by interleukin-1alpha (IL-1alpha) or tumor necrosis factor alpha (TNFalpha) in a time- and concentration-dependent fashion. IL-1alpha was found to be more potent than TNFalpha and each was optimal at 10<sup>-10</sup> mol/L, with a significant (P < .05) effect observed at 1 hour postcytokine incubation that was maximal at 5 hours. IL-1alpha stimulation not only increased the number of SAEC engulfing apoptotic eosinophils, but also enhanced their capacity for ingestion. The amino sugars glucosamine, n-acetyl glucosamine, and galactosamine significantly inhibited uptake of apoptotic eosinophils by both resting and IL-1alpha-stimulated SAEC, in contrast to the parent sugars glucose, galactose, mannose, and fucose. Incubation of apoptotic eosinophils with the tetrapeptide RGDS, but not RGEs, significantly inhibited their uptake by both resting and IL-1alpha-stimulated SAEC, as did **monoclonal** antibody against alpha<sub>v</sub>beta<sub>3</sub> and CD36. Thus, SAEC recognize apoptotic eosinophils via lectin- and **integrin**-dependent mechanisms. These data demonstrate a novel function for human bronchial epithelial cells that might represent an important mechanism in the resolution of eosinophil-induced asthmatic inflammation.

L6 ANSWER 9 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS  
 AN 1999:164861 BIOSIS  
 DN PREV199900164861  
 TI Previous uptake of apoptotic neutrophils or ligation of **integrin** receptors downmodulates the ability of macrophages to ingest apoptotic neutrophils.

AU Erwig, Lars-Peter (1); Gordon, Sharon; Walsh, Garry M.; Rees, Andrew J.  
 CS (1) Univ. Aberdeen, Dep. Med. Therapeutics, Inst. Med. Sci., Foresterhill, Aberdeen AB25 2ZD UK  
 SO Blood, (Feb. 15, 1999) Vol. 93, No. 4, pp. 1406-1412.  
 ISSN: 0006-4971.  
 DT Article  
 LA English  
 AB Clearance of apoptotic neutrophils (polymorphonuclear **leukocyte** (PMN)) by macrophages is thought to play a crucial role in resolution of acute inflammation. There is increasing evidence that ingestion of apoptotic cells modulates macrophage behavior. We therefore performed experiments to determine whether ingestion of apoptotic PMN modulated the uptake process itself. Rat bone marrow-derived macrophages (BMDM) ingested

apoptotic PMN by a process that was enhanced by tumor necrosis factor (TNF) and attenuated by interferon (IFN)-gamma, interleukin (IL)-4, and IL-10. It was inhibitable by the tetrapeptide arg-gly-gln-ser (RGDS), therefore implicating the alphavbeta3/CD36/thrombospondin pathway. Interaction of apoptotic PMN with BMDM for 30 minutes, 48 hours before rechallenger reduced uptake of apoptotic PMN by 50% compared with previously unchallenged BMDM. Blocking initial uptake with RGDS abrogated the effect of preexposure. Comparable and sustained attenuation of uptake was obtained by ligating alphavbeta3 with the **monoclonal** antibody (MoAb), F11, after a delay of more than 90 minutes, whereas

MoAbs

to CD25 and CD45 had no effect. Ligation of alpha6beta1 and alpha1beta2, **integrins** not previously implicated in the engulfment of apoptotic cells also decreased uptake with similar kinetics to F11. Therefore, apoptotic PMN regulate their own uptake through an **integrin**-dependent process, which can be reproduced by ligation of other **integrins** expressed by macrophages.

L6 ANSWER 10 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1999:137648 BIOSIS

DN PREV199900137648

TI Molecular and biochemical mechanisms of Pasteurella haemolytica leukotoxin-induced **cell death**.

AU Wang, Jian Fei; Kieba, Irene R.; Korostoff, Jon; Guo, Tai Liang; Yamaguchi, Noboru; Rozmiarek, Harry; Billings, Paul C.; Shenker, Bruce

J.;

Lally, Edward T. (1)

CS (1) Leon Levy Res. Cent. Oral Biol., Sch. Dental Med., Univ. Pa., 4010 Locust St., Philadelphia, PA 19104-6002 USA

SO Microbial Pathogenesis, (Dec., 1998) Vol. 25, No. 6, pp. 317-331. ISSN: 0882-4010.

DT Article

LA English

AB Pasteurella haemolytica leukotoxin (LKT) is a member of the RFX family of pore-forming toxins that kill bovine immune cells. Several studies have suggested that RTX toxins kill target cells by the induction of **apoptosis**. In the present study, BL3 bovine leukaemia cells were exposed to LKT and assessed by molecular and flow cytometric techniques that measure different aspects of apoptotic **cell death**. The intoxicated cells demonstrated morphological, light scatter and Hoechst 33258 staining characteristics consistent with cells undergoing **apoptosis**. The cells also exhibited internucleosomal DNA fragmentation and poly (ADP-ribose) polymerase (PARP) cleavage, both indicators of **apoptosis**. LKT-treated cells bound annexin-V-FITC indicating that phosphatidylserine groups were translocated from the

inner

to the outer leaflet of the cell membrane. The effect of LKT on cells was dose dependent and inhibitable by incubation with anti-LKT **monoclonal** antibody. Finally, an early step for induction of **apoptosis** appears to be the binding of LKT to a beta2 **integrin** since pre-incubating cells with anti-beta2 **integrin** antibodies inhibited LKT-induced **apoptosis**. This study provides new insights into understanding the pathogenesis of bovine pasteurellosis and could lead to the development of both preventative and therapeutic strategies for disease management.

L6 ANSWER 11 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1998:505448 BIOSIS  
 DN PREV199800505448  
 TI Accutin, a new disintegrin, inhibits angiogenesis in vitro and in vivo by acting as **integrin** alphavbeta3 antagonist and inducing **apoptosis**.  
 AU Yeh, Chia Hsin; Peng, Hui-Chin; Huang, Tur-Fu (1)  
 CS (1) Dep. Pharmacology, Coll. Med., Natl. Taiwan Univ., No. 1, Sec. 1, Jen-Ai Rd., Taipei Taiwan  
 SO Blood, (Nov. 1, 1998) Vol. 92, No. 9, pp. 3268-3276. ISSN: 0006-4971.  
 DT Article  
 LA English  
 AB Endothelial **integrins** play an essential role in angiogenesis and cell survival. Accutin, a new member of disintegrin family derived from venom of Agkistrodon acutus, potently inhibited human platelet aggregation caused by various agonists (e.g., thrombin, collagen, and, adenosine diphosphate (ADP)) through the blockade of fibrinogen binding to platelet glycoprotein IIb/IIIa (i.e., **integrin** alphaIIbbeta3). In this report, we describe that accutin specifically inhibited the binding of **monoclonal** antibody (MoAb) 7E3, which recognizes **integrin** alphavbeta3, to human umbilical vein endothelial cells (HUVECs), but not those of other anti-**integrin** MoAbs such as alpha2beta1, alpha3beta1, and alpha5beta1. Moreover, accutin, but not the control peptide GRGES, dose-dependently inhibited the 7E3 interaction with HUVECs. Both 7E3 and GRGDS, but not GRGES or Integrelin, significantly blocked fluorescein isothiocyanate- conjugated accutin binding to HUVEC. In functional studies, accutin exhibited inhibitory effects on HUVEC adhesion to immobilized fibrinogen, fibronectin and vitronectin, and the capillary-like tube formation on Matrigel in a dose- and RGD-dependent manner. In addition, it exhibited an effective antiangiogenic effect in vivo when assayed by using the 10-day-old embryo chick CAM model. Furthermore, It potently induced HUVEC apoptotic DNA fragmentation as examined by electrophoretic and flow cytometric assays. In conclusion, accutin inhibits angiogenesis in vivo and in vitro by blocking **integrin** alphavbeta3 of endothelial cells and by inducing **apoptosis**. The antiangiogenic activity of disintegrins might be explored as the target of developing the potential antimetastatic agents.

L6 ANSWER 12 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS  
 AN 1998:206632 BIOSIS  
 DN PREV199800206632  
 TI Selective expression of beta7 **integrin** on **lymphocytes** undergoing **apoptosis** in **lymphoid** tissues.  
 AU Akari, Hirofumi (1); Yagita, Hideo; Nishida, Tadashi; Nakamaru, Kenji; Terao, Keiji; Yoshikawa, Yasuhiro; Adachi, Akio  
 CS (1) Dep. Virol., Sch. Med., Univ. Tokushima, 3 Kuramono, Tokushima 770 Japan  
 SO Biochemical and Biophysical Research Communications, (March 17, 1998) Vol. 244, No. 2, pp. 578-582. ISSN: 0006-291X.  
 DT Article  
 LA English  
 AB It has been previously shown that the beta7 chain of **integrin**

forms heterodimers with the alpha4 or alphaE chain, which plays essential roles in **lymphocyte** homing to mucosal **lymphoid** tissues. The aim of this study was to re-evaluate the possible role of the

beta7 **integrin** other than **lymphocyte** homing. We prepared spleen and **lymph** node **lymphocytes** from biopsied specimens from macaque monkeys and examined for the reactivity with a **monoclonal** antibody specific for the beta7 chain. As a result, a minor population of the **lymphocytes** with a smaller size, which were in the early stage of **apoptosis**, was found to express a higher level of the beta7 **integrin** than a majority of the **lymphocytes** with a normal size. Interestingly, the apoptotic **lymphocytes** expressed neither alpha4 nor alphaE chains, suggesting that the beta7 chain on these cells may be associated with an undefined alpha chain. These findings indicate that in the **lymphoid** tissues the shrunken **lymphocytes** undergoing **apoptosis** selectively express a unique beta7 **integrin**.

L6 ANSWER 13 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1998:132488 BIOSIS

DN PREV199800132488

TI Rescue from **apoptosis** in early (CD34-selected) versus late (non-CD34-selected) human hematopoietic cells by very late antigen 4- and vascular cell adhesion molecule (VCAM) 1-dependent adhesion to bone marrow

stromal cells.

AU Wang, Michael W.-J.; Consoli, Ugo; Lane, Cynthia M.; Durett, April; Lauppe, Mary Jo; Champlin, Richard; Andreeff, Michael; Deisseroth, Albert B. (1)

CS (1) Yale Comprehensive Cancer Cent., Yale Univ. Sch. Med., 333 Cedar Street, New Haven, CT 06520-8032 USA

SO Cell Growth & Differentiation, (Feb., 1998) Vol. 9, No. 2, pp. 105-112. ISSN: 1044-9523.

DT Article

LA English

AB **Monoclonal** antibodies to very late antigen 4 (VLA-4) recognize the alpha4betal **integrin** receptor. This **monoclonal** antibody blocks the adhesion between early hematopoietic progenitor cells (CD34-selected cells) and stromal cells when added to cultures of these cells. Addition of the VLA-4 **monoclonal** antibody to cultures of stromal cells and CD34-selected cells was shown to induce **apoptosis** of CD34-selected cells in these CD34-selected cell/stromal cell cocultures, as measured by the terminal deoxynucleotidyltransferase-mediated dUTP-biotin nick end-labeling

method.

In contrast to these experiments with early hematopoietic progenitor cells

(CD34+), the level of adhesion between more differentiated cells (unfractionated hematopoietic cells) and stromal cells was not significantly altered by addition of the anti-VLA-4 **monoclonal** antibody. Similarly, the level of **apoptosis** of unfractionated hematopoietic cells was not significantly increased by the addition of anti-VLA-4 **monoclonal** antibody to cultures of the latter cells with stromal cells. The binding of the unfractionated cells is less than that of the CD34-selected cells. Given that there is no difference

between

the alpha4betal **integrin** expression level of the early and late

myeloid cells, there may be a difference in the functional state of the **integrin** between the early and late myeloid cells. We also show that CD34+-selected precursor cells proliferate at a higher rate when these cells are plated on recombinant vascular cell adhesion molecule 1 molecules. These data indicate that the alpha4beta1 **integrin** receptor (VLA-4) plays a central role in the **apoptosis** rescue function that results from the anchorage-dependent growth of the CD34-selected early hematopoietic cells on stromal cells. The data suggest that these **apoptosis** rescue pathways have less significance as the cells mature and become anchorage independent in their growth. These data should assist in the design of systems for the ex vivo proliferation and transduction of early hematopoietic cells for genetic therapy.

L6 ANSWER 14 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS  
 AN 1997:454857 BIOSIS  
 DN PREV199799754060  
 TI High levels of a major histocompatibility complex II-self peptide complex on dendritic cells from the T cell areas of **lymph** nodes.  
 AU Inaba, Kayo; Pack, Manggie; Inaba, Muneo; Sakuta, Hiraki; Isdell, Frank; Steinman, Ralph M. (1)  
 CS (1) Rockefeller Univ., 1230 York Avenue, New York, NY 10021 USA  
 SO Journal of Experimental Medicine, (1997) Vol. 186, No. 5, pp. 665-672. ISSN: 0022-1007.  
 DT Article  
 LA English  
 AB T **lymphocytes** recirculate continually through the T cell areas of peripheral **lymph** nodes. During each passage, the T cells survey the surface of large dendritic cells (DCs), also known as interdigitating cells. However, these DCs have been difficult to release from the **lymph** node. By emphasizing the use of calcium-free media, as shown by Vremec et al. (Vremec, D., M. Zorbas, R. Scollay, D.J. Saunders, C.F. Ardavin, L. Wu, and K. Shortman. 1992. J. Exp. Med. 176:47-58.), we have been able to release and enrich DCs from the T cell areas. The DCs express the CD11c **leukocyte integrin**, the DEC-205 multilectin receptor for antigen presentation, the intracellular granule antigens which are recognized by **monoclonal** antibodies M342, 2A1, and MIDC-8, very high levels of MHC I and MHC II, and abundant accessory molecules such as CD40, CD54, and CD86. When examined with the Y-Ae **monoclonal** which recognizes complexes formed between I-Ab-b and a peptide derived from I-E-alpha, the T cell area DCs expressed the highest levels. The enriched DCs also stimulated a T-T hybridoma specific for this MHC II-peptide complex, and the hybridoma underwent **apoptosis**. Therefore DCs within the T cell areas can be isolated. Because they present very high levels of self peptides, these DCs should be considered in the regulation of self reactivity in the periphery.

L6 ANSWER 15 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS  
 AN 1997:454722 BIOSIS  
 DN PREV199799753925  
 TI **Integrin** regulation of polymorphonuclear **leukocyte** apoptosis during hypoxia is primarily dependent on very late activation antigens 3 and 5.  
 AU Leuenroth, Stephanie; Isaacson, Ernest; Lee, Christine; Keeping, Hugh; Simms, H. Hank (1)

CS (1) Rhode Island Hosp., Dep. Surg., 593 Eddy St., Providence, RI 02903  
USA

SO Surgery (St Louis), (1997) Vol. 122, No. 2, pp. 153-162.  
ISSN: 0039-6060.

DT Article

LA English

AB Background. **Apoptosis** is thought to be a central mechanism that leads to resolution of the inflammatory response. The regulation of polymorphonuclear **leukocyte** (PMN) **apoptosis** during hypoxia has not been previously characterized, and we hypothesized that **integrin** signaling by matrix proteins (laminin) would regulate PMN **apoptosis**. Methods. PMNs at 1 times 10<sup>5</sup>/ml were adhered on plastic or laminin for 12 hours during normoxia or hypoxia. **Apoptosis** was determined both by cellular histologic evaluation and the TUNEL assays (Tdt). Phagocytosis in apoptotic PMNs was determined with two-color flow cytometric analyses with rhodamine-labeled heat-killed

Escherichia coli (511 nm) and the Tdt reagent (563 nm). Western blot analyses were performed on nine apoptotic regulatory proteins with **monoclonal** antibodies directed against each protein, and tyrosine phosphorylation was assessed after **integrin** receptor cross-linkage. Results. Adherence of PMNs to laminin reduced **apoptosis** by cellular histologic evaluation and the Tdt method (% **apoptosis** = 19 ± 1.0 versus 63 ± 4.2 by histologic evaluation, 38 ± 3.8 versus 60 ± 10.5 by flow cytometry ± adherence to laminin). **Apoptosis**-positive PMNs exhibited significantly greater phagocytosis than **apoptosis**-negative PMNs ± laminin. Western blot analyses demonstrated increased p53 expression after 2 and 4 hours

of hypoxia. Cross-linkage of very late activation antigen-3 (alpha-3/beta-1) resulted in the phosphorylation of 53 kd, 44 kd, and 39 kd proteins at 30 seconds. Conclusions. (1) Chemotaxis of PMNs into the interstitium during hypoxia not only provides a means of ensuring PMN-pathogen contact but also provides a mechanism for improved survival by reducing **apoptosis**. (2) The reduction of **apoptosis** is mediated primarily by very late activation antigen-3, which leads to a subsequent increase in the intracellular expression of p53 and increased bacterial phagocytosis.

L6 ANSWER 16 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1997:434440 BIOSIS

DN PREV199799733643

TI **Leukocyte** contribution to parenchymal **cell death** in an experimental model of inflammation.

AU Tung, David K.-L.; Bjursten, Lars M.; Zweifach, Benjamin W.; Schmid-Schonbein, Geert W.

CS Dep. Bioengineering, Inst. Biomed. Engineering, Univ. California, San Diego, La Jolla, CA 92093-0412 USA

SO Journal of Leukocyte Biology, (1997) Vol. 62, No. 2, pp. 163-175.  
ISSN: 0741-5400.

DT Article

LA English

AB The relationship between **leukocyte** migration and parenchymal **cell death** in vivo remains poorly documented. Accordingly, cell killing in the rat mesentery, as recorded by propidium iodide staining, was investigated with an intravital approach.

Superfusion

of platelet-activating factor (PAF,  $10^{-8}$  M) or N-formyl-methionyl-leucyl-phenylalanine (fMLP,  $10^{-8}$  M) led to extensive **leukocyte** extravasation but no significant **cell death**. In contrast, pretreatment with  $10^{-8}$  M PAF or fMLP for 1 h, followed by superfusion of PAF in combination with fMLP (both at  $10^{-8}$  M) led to an increase in **cell death**. Mesenteric parenchymal cells but no endothelial cells were killed. Some of the dead cells were identified as granulocytes/**monocytes** that were already in the tissue at the start of the experiment. The incidence of **cell death** was lower but not eliminated when **leukocyte** migration was blocked with a **monoclonal** antibody against CD18. A xanthine oxidase inhibitor, BOF-4272, failed to diminish **cell death**, whereas a hydroxyl radical scavenger, dimethylthiourea, attenuated cell killing without an effect on the number of adhering and migrating **leukocytes**. These observations demonstrate that **leukocytes** serve as a factor in the killing of extravascular cells only after the development of a level of stimulation that differs from that required to induce a migratory stimulus into the extravascular

space.

L6 ANSWER 17 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS  
 AN 1997:167950 BIOSIS  
 DN PREV199799474553  
 TI CD30 ligand is frequently expressed in human hematopoietic malignancies of myeloid and **lymphoid** origin.  
 AU Gattei, Valter (1); Degan, Massimo; Gloghini, Annunziata; De Luliis, Angela; Improta, Salvatore; Rossi, Francesca Maria; Aldinucci, Donatella; Perin, Vilma; Serraino, Diego; Babare, Roberta; Zagonel, Vittorina; Gruss, Hans-Juergen; Carbone, Antonino; Pinto, Antonio  
 CS (1) Leukemia Unit, Dep. Med. Oncol., Cent. Regionale Riferimento Oncol., IRCCS, Via Pedemontana Occidentale, I-33081 Aviano Italy  
 SO Blood, (1997) Vol. 89, No. 6, pp. 2048-2059.  
 ISSN: 0006-4971.  
 DT Article  
 LA English  
 AB CD30 ligand (CD30L) is a type-II membrane glycoprotein capable of transducing signals leading to either **cell death** or proliferation through its specific counterstructure CD30. Although several lines of evidence indicate that CD30L plays a key role as a paracrine- or autocrine-acting surface molecule in the deregulated cytokine cascade of Hodgkin's disease, little is known regarding its distribution and biologic significance in other human hematopoietic malignancies. By analyzing tumor cells from 181 patients with RNA studies and immunostaining by the anti-CD30L **monoclonal** antibody M80, we were able to show that human hematopoietic malignancies of different lineage and maturation stage display a frequent and broad expression of the ligand. CD30L mRNA and surface protein were detected in 60% of acute myeloid leukemias (AMLs), 54% of B-lineage acute **lymphoblastic** leukemias (ALLs), and in a consistent fraction (68%) of B-cell **lymphoproliferative** disorders. In this latter group, hairy cell **leukemia** and high-grade B-cell non-Hodgkin's **lymphoma** (B-NHL) expressed a

higher surface density of CD30L as compared with B-cell chronic **lymphocytic leukemia** and low-grade B-NHL. Purified plasmacells from a fraction of multiple myeloma patients also displayed CD30L mRNA and protein. A more restricted expression of CD30L was found

in

T-cell tumors that was mainly confined to neoplasms with an activated peripheral T-cell phenotype, such as T-cell prolymphocytic **leukemia**, peripheral T-NHL, and adult T-cell **leukemia/lymphoma**. In contrast, none of the T-lineage ALLs analyzed expressed the ligand. In AML, a high cellular density of CD30L was detected in French-American-British M3, M4, and M5 phenotypes, which are directly associated with the presence on tumor cells of certain surface structures, including the p55 interleukin-2 receptor alpha-chain, the  $\alpha$  chain of beta-2 **integrins**, and the intercellular adhesion molecule-1 (CD54). Analysis of normal hematopoietic cells evidenced that, in addition to circulating and tonsil B cells, a fraction of bone marrow myeloid precursors, erythroblasts, and subsets of megakaryocytes also express CD30L. Finally, we have shown that native CD30L expressed on primary leukemic cells is functionally active by triggering both mitogenic and antiproliferative signals on CD30+ target cells. As opposed to CD30L, only 10 of 181 primary tumors expressed CD30 mRNA or protein, rendering therefore unlikely a CD30-CD30L autocrine loop in human hematopoietic neoplasms. Taken together, our data indicate that CD30L is widely expressed from early to late stages of human

hematopoiesis

and suggest a regulatory role for this molecule in the interactions of normal and malignant hematopoietic cells with CD30+ immune effectors and/or microenvironmental accessory cells.

L6 ANSWER 18 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1997:128928 BIOSIS

DN PREV199799420741

TI Protection from **apoptosis** in human neutrophils is determined by the surface of adhesion.

AU Ginis, Irene; Faller, Douglas V. (1)

CS (1) Cancer Res. Cent. E-124, Boston Univ. Sch. Medicine, 80 E. Concord St., Boston, MA 02118 USA

SO American Journal of Physiology, (1997) Vol. 272, No. 1 PART 1, pp. C295-C309.

ISSN: 0002-9513.

DT Article

LA English

AB Recent work suggests that various neutrophil agonists affect the rate of **apoptosis** in these cells. On the basis of these observations, we hypothesized that signals triggered in neutrophils via their adhesion receptors might also modify their life span. This hypothesis has been tested using human neutrophils adherent to tissue culture plastic, either untreated or coated with extracellular matrix (ECM) proteins or with monolayers of human umbilical vein endothelial cells. To detect and quantitate apoptotic changes in adherent cells, we developed a microtiter plate assay using a cell-permeable DNA-binding fluorescent dye, Hoechst 33342. Use of this assay demonstrated that 1) the number of apoptotic cells among neutrophils adherent to plastic after 6-20 h of incubation

was

significantly lower than that among neutrophils adherent to the ECM proteins fibronectin or laminin; 2) adhesion to interleukin-1-activated endothelial cells delayed **apoptosis**, whereas adhesion to

nonactivated endothelium accelerated neutrophil death; and 3) **monoclonal** antibodies directed against intercellular adhesion molecule 1 or against the common beta-2-chain of the **leukocyte integrins** abolished the protective effect of interleukin-1-activated endothelial cells on **apoptosis** of adherent neutrophils. These results suggest that the life span of adherent neutrophils depends on the activating signals triggered by the surface of adhesion.

L6 ANSWER 19 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS  
 AN 1996:570608 BIOSIS  
 DN PREV199799285289  
 TI Characterization of a CD43/Leukosialin-mediated pathway for inducing **apoptosis** in human T-**lymphoblastoid** cells.  
 AU Brown, T. Joseph; Shuford, Walt W.; Wang, Wei-Chun; Nadler, Steven G.; Bailey, Tina S.; Marquardt, Hans; Mittler, Robert S. (1)  
 CS (1) 3005 First Ave., Seattle, WA 98121 USA  
 SO Journal of Biological Chemistry, (1996) Vol. 271, No. 44, pp. 27686-27695.  
 ISSN: 0021-9258.  
 DT Article  
 LA English  
 AB The **monoclonal** antibody (mAb) J393 induces **apoptosis** in Jurkat T-cells. NH-2-terminal amino acid sequence analysis identified the 140-kDa surface antigen for mAb J393 as CD43/leukosialin, the major sialoglycoprotein of **leukocytes**. While Jurkat cells co-expressed two discrete cell-surface isoforms of CD43, recognized by mAb J393 and  
 mAb G10-2, respectively, only J393/CD43 signaled **apoptosis**. J393/CD43 was found to be hyposialylated, bearing predominantly O-linked monosaccharide glycans, whereas G10-2/CD43 bore complex sialylated tetra- and hexasaccharide chains. Treatment with soluble, bivalent raAb J393 killed 25-50% of the cell population, while concomitant engagement of either the CD3 cntdot TcR complex or the **integrins** CD18 and CD29 significantly potentiated this effect. Treatment of Jurkat cells with mAb J393 induced tyrosine phosphorylation of specific protein substrates that underwent hyperphosphorylation upon antigen receptor costimulation. Tyrosine kinase inhibition by herbimycin A diminished J393/CD43-mediated **apoptosis**, whereas inhibition of phosphotyrosine phosphatase activity by bis(maltolato) oxovanadium-IV enhanced **cell death**. Signal transduction through tyrosine kinase activation may lead to altered gene expression, as J393/CD43 ligation prompted decreases in the nuclear localization of the transcriptional regulatory protein NF-kappa-B and proteins binding the interferon-inducible regulatory element. Since peripheral **blood T-lymphocytes** express cryptic epitopes for mAb J393, these findings demonstrate the existence  
 of a tightly regulated CD43-mediated pathway for inducing **apoptosis** in human T-cell lineages.

L6 ANSWER 20 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS  
 AN 1996:485221 BIOSIS  
 DN PREV199699200477  
 TI Human **monocyte**-derived macrophage phagocytosis of senescent eosinophils undergoing **apoptosis**: Mediation by alpha-v-beta-3/CD36/thrombospondin recognition mechanism and lack of phlogistic response.

AU Stern, Myra; Savill, John (1); Haslett, Chris  
 CS (1) Div. Renal Inflammatory Diseases, Dep. Med., Univ. Hosp., Nottingham  
 NG7 2UH UK  
 SO American Journal of Pathology, (1996) Vol. 149, No. 3, pp. 911-921.  
 ISSN: 0002-9440.  
 DT Article  
 LA English  
 AB Eosinophils may mediate tissue injury in a number of allergic diseases.  
 Previously, we reported that eosinophils constitutively undergo  
**apoptosis** (programmed **cell death**) in culture.  
 As this led to phagocytosis of the intact senescent cell by macrophages,  
 we proposed that **apoptosis** represented an injury-limiting  
 eosinophil disposal mechanism. Ingestion of apoptotic neutrophils by  
 human **monocyte**-derived macrophages (M-PHI-s) was found to be mediated by  
 adhesive interactions between thrombospondin and the MO alpha-v-beta-3  
 vitronectin receptor **integrin** and MO CD36. As this failed to  
 elicit a pro-inflammatory response from M-PHI-s, we sought evidence that  
 this specific, nonphlogistic clearance mechanism may operate in  
 eosinophil disposal. In this study, we found that M-PHI ingestion of apoptotic  
 eosinophils was specifically inhibited by **monoclonal** antibodies  
 to M-PHI alpha-v-beta-3, CD36, and thrombospondin and by other inhibitors  
 of this recognition mechanism including RGD peptide and amino sugars.  
 Furthermore, not only did M-PHI ingestion of intact apoptotic eosinophils  
 fail to stimulate release of the phlogistic eicosanoid thromboxane, but  
 there was also a lack of increased release of the pro-inflammatory  
 cytokine granulocyte/macrophage colony-stimulating factor. However,  
 increased release of these mediators was observed when M-PHI-s took up  
 senescent post-apoptotic eosinophils that had been cultured long enough  
 to lose plasma membrane integrity. The data indicate that the nonphlogistic  
 alpha-v-beta-3/CD36/thrombospondin macrophage recognition mechanism is  
 available for clearance of intact senescent eosinophils undergoing  
**apoptosis**. Furthermore, our findings suggest that, by contrast,  
 phagocytosis of post-apoptotic eosinophils may elicit undesirable  
 pro-inflammatory responses.

L6 ANSWER 21 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS  
 AN 1996:480223 BIOSIS  
 DN PREV199699195479  
 TI **Apoptosis** following interleukin-2 withdrawal from T cells:  
 Evidence for a regulatory role of CD18 (beta-2-**integrin**)  
 molecules.

AU Ropke, C.; Gladstone, P.; Nielsen, M.; Borregard, N.; Ledbetter, J. A.;  
 Svejgaard, A.; Odum, N. (1)  
 CS (1) Cell Cybernetics Lab., Inst. Med. Microbiol. Immunol., Panum 22.5.34,  
 Univ. Copenhagen, Blegdamsvej 3, DK-2200 Copenhagen N Denmark  
 SO Tissue Antigens, (1996) Vol. 48, No. 2, pp. 127-135.  
 ISSN: 0001-2815.  
 DT Article  
 LA English  
 AB Following a successful immune response against invading microorganisms,  
 the majority of activated T cells is eliminated, while a minor fraction  
 survives as memory T cells. A decline in T **lymphocyte** growth  
 factors such as interleukin-2 (IL-2) appears to play a role in the  
 elimination of previously activated T cells. Thus, removal of IL-2 from

proliferating T cells not only induces growth arrest, but triggers a massive **cell death** due to **apoptosis**. While the apoptotic response involves a series of well-described events, it remains less clear how **apoptosis** is regulated following IL-2 withdrawal. Here, we provide evidence that CD18 molecules (beta-2-**integrins**) play a regulatory role in the apoptotic response following removal of IL-2 from previously activated, antigen specific

CD4+

T cell lines. Thus, CD18 mAb inhibited the apoptotic response to IL-2 deprivation, whereas mAb against other adhesion molecules (CD28, CD29, CD49d, CD80, CD86) did not. Secondly, IL-2 withdrawal resulted in a retarded apoptotic response in LFA-1 (CD11a/CD18) negative T cells obtained from a **leukocyte** adhesion deficiency (LAD) patient, as compared to LFA-1 positive T cell lines. Thirdly, co-culture of LFA-1 positive- and negative-T cells at different ratios induced apoptotic responses that were higher than expected, had the two **lymphocyte** populations not been interacting and significantly higher than that seen in pure LFA-1 negative T cells. Supernatants from LFA-1 positive T cell cultures undergoing **apoptosis** did not induce an enhanced apoptotic responses in LFA-1 negative T cells, and, reversely, culture supernatants from LFA-1 negative T cells did not rescue LFA-1 positive cells from undergoing **apoptosis**. The apoptotic response was partly blocked by IL-15, a newly identified T cell growth factor. Taken together, these findings suggest that CD18 molecules (beta-2-**integrins**) play a regulatory role in the apoptotic response following cytokine withdrawal, and that the regulation is mediated, at least partly, through T-T **cell** interactions. Thus, apoptotic **death** following IL-2 deprivation appears to be under "social" control by surrounding T cells.

- L6 ANSWER 22 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS  
 AN 1996:254265 BIOSIS  
 DN PREV199698810394  
 TI Role of VLA-4 and VCAM-1 in regulation of the **apoptosis** of immature (CD34 selected) versus mature (CD34 unselected) human hematopoietic precursor cells by adhesion to bone marrow stromal cells.  
 AU Wang, W.-J. M.; Consoli, U.; Berenson, R.; Heimfeld, S.; Andreeff, M.; Deisseroth, A. B.  
 CS Univ. Texas MD Anderson Cancer Cent., Houston, TX 77030 USA  
 SO Proceedings of the American Association for Cancer Research Annual Meeting, (1996) Vol. 37, No. 0, pp. 22-23.  
 Meeting Info.: 87th Annual Meeting of the American Association for Cancer Research Washington, D.C., USA April 20-24, 1996  
 ISSN: 0197-016X.  
 DT Conference  
 LA English
- L6 ANSWER 23 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS  
 AN 1995:478535 BIOSIS  
 DN PREV199598492835  
 TI Costimulation of CD3/TcR complex with either **integrin** or nonintegrin ligands protects CD4+ allergen-specific T-cell clones from programmed **cell death**.  
 AU Agea, E.; Bistoni, O.; Bini, P.; Migliorati, G.; Nicoletti, I.; Bassotti, G.; Riccardi, C.; Bertotto, A.; Spinozzi, F. (1)  
 CS (1) Inst. Med. Interna Sci. Oncol., Policlin. Montelucente, I-06100 Perugia Italy

SO Allergy (Copenhagen), (1995) Vol. 50, No. 8, pp. 677-682.  
ISSN: 0105-4538.

DT Article

LA English

AB An optimal stimulation of CD4+ cells in an immune response requires not only signals transduced via the TcR/CD3 complex, but also costimulatory signals delivered as a consequence of interactions between T-cell surface-associated costimulatory receptors and their counterparts on antigen-presenting cells (APC). The intercellular adhesion molecule-1 (ICAM-1, CD54) efficiently costimulates proliferation of resting, but not antigen-specific, T cells. In contrast, CD28 and CD2 support interleukin (IL)-2 synthesis and proliferation of antigen-specific T cells more efficiently than those of resting T cells. The molecular basis for this differential costimulation of T cells is poorly understood. Cypress-specific T-cell clones (TCC) were generated from four allergic subjects during in vivo seasonal exposure to the allergen. Purified cypress extract was produced directly from fresh collected pollen and incubated with the patients' mononuclear cells. Repeated allergen stimulation was performed in T-cell cultures supplemented with purified extract and autologous APC. The limiting-dilution technique was then adopted to generate allergen-specific TCC, which were also characterized by their cytokine secretion pattern as Th0 (IL-4 plus interferon-gamma)

or

Th2 (IL-4). Costimulation-induced proliferation or **apoptosis** was measured by propidium iodide cytofluorometric assay. By cross-linking cypress-specific CD4+ and CD8+ T-cell clones with either anti-CD3 or anti-CD2, anti-CD28, and anti-CD54 **monoclonal** antibodies, we demonstrated that CD4+ clones (with Th0- or Th2-type cytokine production pattern) undergo programmed **cell death** only after anti-CD3 stimulation, whereas costimulation with either anti-CD54 or anti-CD28 protects target cells from **apoptosis**. The costimulation-induced protection from apoptotic death was associated with a significant rise in IL-4 secretion in both Th0 and Th2-type clones. In contrast, cypress-specific Th0 CD8 clones were more susceptible to stimulation-induced **apoptosis** via either anti-CD3 or anti-CD2, alone or in combination with anti-CD54 or anti-CD28, thus displaying only slight but nonsignificant modifications in the pattern of IL-4 secretion. The death-promoting costimulatory effects were not observed with highly purified normal resting CD4+ or CD8+ **lymphocytes**. Taken together, these results suggest that TcR engagement by an allergen in the context of functionally active APC induces activation-dependent **cell death** of some, perhaps less specific, cells, and this may be an important homeostatic mechanism through which functional expansion of allergen-specific T cells is regulated during an ongoing immune response.

L6 ANSWER 24 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1995:80772 BIOSIS

DN PREV199598095072

TI **Integrin** alpha-v-beta-3 antagonists promote tumor regression by inducing **apoptosis** of angiogenic **blood** vessels.

AU Brooks, Peter C. (1); Montgomery, Anthony M. P. (1); Rosenfeld, Mauricio (1); Reisfeld, Ralph A. (1); Hu, Tianhua; Klier, George; Cheresch, David

A.

(1)

CS (1) Dep. Immunol., Scripps Research Inst., La Jolla, CA 92037 USA

SO Cell, (1994) Vol. 79, No. 7, pp. 1157-1164.

ISSN: 0092-8674.

DT Article

LA English

AB A single intravascular injection of a cyclic peptide or **monoclonal** antibody antagonist of **integrin** alpha-v-beta-3 disrupts ongoing angiogenesis on the chick chorioallantoic membrane (CAM). This leads to the rapid regression of histologically distinct human tumors transplanted onto the CAM. Induction of angiogenesis by a tumor or cytokine promotes vascular cell entry into the cell **apoptosis** of the proliferative angiogenic vascular cells, leaving preexisting quiescent **blood** vessels unaffected. We demonstrate therefore that ligation of **integrin** alpha-v-beta-3 is required for the survival and maturation of newly forming **blood** vessels, an event essential for the proliferation of tumors.

L6 ANSWER 25 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1993:523547 BIOSIS

DN PREV199396136954

TI Mitosis and **apoptosis** of microglia in vivo induced by an anti-CR3 antibody which crosses the **blood**-brain barrier.

AU Reid, D. M. (1); Perry, V. H.; Andersson, P.-B.; Gordon, S.

CS (1) Univ. Dep. Pharmacol., Mansfield Rd., Oxford UK

SO Neuroscience, (1993) Vol. 56, No. 3, pp. 529-533.

ISSN: 0306-4522.

DT Article

LA English

AB Microglia, the resident tissue macrophages of the central nervous system, have a highly differentiated morphology and do not express many of the antigens typically associated with other tissue macrophages. Activation

of

many microglia is associated with a change in morphology and an increase in their repertoire of antigen expression. Microglia become activated in

neuropathological conditions including chronic neurodegenerative diseases and human immunodeficiency virus neuropathology, yet little is known of the mechanisms involved. Here we demonstrate for the first time that microglia can be activated and induced to divide and/or undergo **apoptosis** via a beta-2-**integrin** (complement receptor type 3, CR3, Mac-1 or CD11b/CD18) using an anti-CR3 **monoclonal** antibody (McAb5C6). This antibody, which has been shown to block myelomonocytic recruitment during central nervous system inflammation, is unique in that it can cross the intact **blood**-brain barrier to activate microglia. Since CR3 not only binds the iC3b component of the alternative complement cascade but also denatured proteins this suggests

a

potential route for microglia activation in neuropathological conditions.

L6 ANSWER 26 OF 26 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1993:480852 BIOSIS

DN PREV199396114452

TI Cell cycle specific effects of tumor necrosis factor alpha in **monocyte** mediated leukemic **cell death** and the role of beta-2-**integrins**.

AU Van De Loosdrecht, Arjan A. (1); Ossenkoppele, Gert J.; Beelen, Robert H. J.; Broekhoven, Marjolein G.; Langenhuijsen, Mart M. A. C.

CS (1) Dep. Hematol., Academisch Ziekenhuis Vrije Univ., De Boelelaan 1117, 1081 HV Amsterdam Netherlands

SO Cancer Research, (1993) Vol. 53, No. 18, pp. 4399-4407.  
ISSN: 0008-5472.

DT Article  
LA English  
AB Human **monocytes** are involved in host defense against neoplastic cells. In view of cellular immunotherapy with cytotoxic **monocytes** in minimal residual disease of acute myeloid **leukemia** we have studied the role of **monocytes** in cell cycle dependent leukemic **cell death** of U937, THP-1, and HL-60 cells in vitro. Leukemic cells separated in G-1 of the cell cycle by countercurrent centrifugal elutriation were highly susceptible to **monocyte** mediated cytotoxicity, whereas cells in S and G-2-M were less sensitive

or completely resistant as compared to unfractionated control cells. HL-60 cells resistant to cytotoxic **monocytes** became sensitive to **monocyte** mediated cytotoxicity upon differentiation induction with 1,25-dihydroxyvitamin D-3 which paralleled an accumulation of cells in

G-1 of the cell cycle. The differences in susceptibility of cell phase separated populations to **monocyte** mediated cytotoxicity paralleled differences in sensitivity to the cytotoxic effects of tumor necrosis factor alpha, as secreted by gamma-interferon activated **monocytes**. Furthermore, **monocyte** mediated cytotoxicity was markedly inhibited in the presence of anti-CD11/CD18 **monoclonal** antibodies recognizing the alpha and beta chains of the beta-2-**integrin** adhesion proteins. By fluorescence activated cell sorter immunofluorescence a marked increase in mean fluorescence density of the beta-2-**integrins** could be demonstrated on cells in G-1 of the cell cycle as compared to unseparated leukemic cells. A decrease in mean fluorescence density was shown for cells in G-2-M. By blocking experiments with anti-CD11/CD18 **monoclonal** antibodies, the differences in mean fluorescence density were functionally relevant since cells in G-1 were shown to be the most sensitive cells to beta-2-**integrin** dependent **monocyte** mediated cytotoxicity. In conclusion these data show that differences in sensitivity to tumor necrosis factor and in the expression of beta-2-**integrins** may play a central role in cell cycle dependent **monocyte** mediated antileukemic activity.

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FILE 'BIOSIS' ENTERED AT 10:10:29 ON 18 JAN 2001

L1 69769 S APOPTOSIS OR CELL (3A) DEATH  
L2 145631 S MONOCLONAL#  
L3 18090 S INTEGRIN# OR IAP#  
L4 45 S L1 AND L2 AND L3  
L5 1577766 S BLOOD# OR LYMPH? OR MYELOCYT? OR LEUKEMIA OR MONOCYT? OR  
LEUK  
L6 26 S L4 AND L5

FILE 'BIOSIS' ENTERED AT 10:13:03 ON 18 JAN 2001